Metabolic Abnormalities in Children with Asthma

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Rationale: Childhood asthma and obesity have reached epidemic proportions worldwide, and the latter is also contributing to increasing rates of related metabolic disorders, such as diabetes. Yet, the relationship between asthma, obesity, and abnormal lipid and glucose metabolism is not well understood, nor has it been adequately explored in children.

Objectives: To analyze the relationship between asthma diagnosis and body mass in children across the entire range of weight percentile categories, and to test the hypothesis that early derangement in lipid and glucose metabolism is independently associated with increased risk for asthma.

Methods: Cross-sectional analysis of a representative sample of public school children from a statewide community-based screening program, including a total of 17,994 children, 4 to 12 years old, living in predominantly rural West Virginia, and enrolled in kindergarten, second, or fifth grade classrooms.

Measurements and Main Results: We analyzed demographics; family history; smoke exposure; parent-reported asthma diagnosis; body mass index; evidence of acanthosis nigricans as a marker for developing insulin resistance; and fasting serum lipid profile including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Regardless of their body mass index percentile, children diagnosed with asthma were more likely than children without asthma to have higher triglyceride levels and acanthosis nigricans after controlling for sex differences and smoke exposure.

Conclusions: This study provides the first set of community-based data linking asthma, body mass, and metabolic variables in children. In particular, these findings uniquely describe a statistically significant association between asthma and abnormal lipid and glucose metabolism beyond body mass index associations.

Keywords: body mass index; cardiovascular risk; diabetes; insulin resistance; obesity

Four million children under 14 years of age have been diagnosed with asthma in the United States (1) and the current global estimates of asthma prevalence range from less than 5% to more than 25% (2). Likewise, childhood obesity has reached epidemic proportions worldwide, prompting First Lady Michelle Obama to launch the "Let's Move!" campaign against childhood obesity in

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Childhood asthma and obesity have reached epidemic proportions worldwide, and the latter is also contributing to increasing rates of related metabolic disorders, such as diabetes. Yet, the relationship between asthma, obesity, and abnormal lipid and glucose metabolism is not well understood.

What This Study Adds to the Field

This study provides the first set of community-based data linking asthma, body mass, and metabolic variables in children. In particular, these findings uniquely describe a significant association between asthma and abnormal lipid and glucose metabolism beyond body mass index associations.

February 2010 (3). Growing awareness of the impact of weight on chronic diseases (4, 5), combined with the evidence of a parallel rise in both obesity and asthma rates among children, has led many to postulate a relationship between these pathologies (6–9). However, it remains controversial whether such a relationship is causal or confounded by other factors.

Previous studies of the association between asthma and obesity have focused on the mechanical effects of abdominal fat on respiratory system compliance (7, 8); on the role of specific nutrients, such as antioxidants and saturated fat (6); and on the inflammatory pathways implicated in both conditions (7, 10). Much of this literature focuses on obesity as the central hub from which complications, such as asthma, cardiovascular disease, and metabolic syndrome, originate. Perhaps as a result of this bias, most of the studies designed to examine the interactions between childhood asthma and obesity were based on select cohorts of children who are obese. Although this strategy is valuable to identify trends within an at-risk group, new and important information could result from studies looking at larger, more heterogeneous samples of children stratified by body mass. Also, an association between childhood asthma and metabolic risk factors independent of obese body mass has not been studied among children and may identify potential confounding factors.

Among the metabolic comorbidities frequently associated with obesity, dyslipidemia and hyperinsulinemia can influence both innate and adaptive defense mechanisms in the respiratory tract, thus promoting the expression of multiple proinflammatory cytokines and chemokines, reduced endogenous antiinflammatory activity, and increased bronchomotor tone (11). Because these events are involved in the pathophysiology of airway inflammation and hyperreactivity, it is conceivable that early life abnormalities in lipid or glucose metabolism may contribute to the pathogenesis of asthma in childhood.

The original goal of this project was to analyze the relationship between asthma diagnosis and body mass in a community-

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Some of the findings reported in this paper were presented at the International Conference of the American Thoracic Society in 2009 (San Diego, CA) and 2010 (New Orleans, LA).

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based sample of children across the entire range of weight percentile categories from underweight to morbidly obese. To this end, we gathered demographic data and estimates of body mass index (BMI) and asthma prevalence in a sample of more than 17,000 children of both sexes and age ranging from 4 to 12 years. Because these children were participating in a comprehensive cardiovascular risk detection screening program, we also had access to their metabolic data, including fasting serum levels of total cholesterol; low-density lipoprotein (LDL) cholesterol; high-density lipoprotein (HDL) cholesterol; triglycerides; and evidence of acanthosis nigricans (AN), a brown to black hyperpigmented skin rash used as a biomarker for developing insulin resistance and hyperinsulinemia. Analyzing metabolic variables in this large and heterogeneous pediatric population, we noted striking associations of asthma prevalence with triglyceride levels and AN, which led us to test the hypothesis that early metabolic dysfunction, and not unhealthy weight *per se*, is associated with airway inflammation and childhood asthma.

Some of the results of these studies have been previously reported in the form of abstracts (12, 13).

METHODS

Additional information on the methods is provided in the online supplement.

Subjects

We studied children enrolled during the 2007–2008 academic year in public schools throughout the state of West Virginia and participating in the Coronary Artery Risk Detection In Appalachian Communities (CARDIAC) Project, a community-based cardiovascular risk detection program (14, 15). All children enrolled in kindergarten, second, and fifth grade classrooms in West Virginia were eligible to participate in CARDIAC. Parental consent and child assent (for second and fifth grade students only) were required to enter this study and all procedures were approved by the West Virginia University Institutional Review Board. Before screening day, participating parents provided demographic and family history information by completing a questionnaire.

BMI

During screening day, children's height and weight were measured using a SECA Road Rod stadiometer and a SECA 840 digital scale (Seca Corp., Hanover, MD). BMI for each child was calculated using the equation recommended by the US Centers for Disease Control and Prevention:

$$\text{BMI} \left(\frac{\text{kg}}{\text{m}^2} \right) = \frac{\text{weight}(\text{kg})}{\text{height}(\text{m})^2}$$

All BMI percentile categories were based on age- and sex-specific growth charts recommended by the Centers for Disease Control and Prevention (16), and were defined as follows: underweight less than 5th percentile; healthy weight 5th to 84.9th percentile; overweight 85th to 94.9th percentile; obese 95th to 98.9th percentile; morbidly obese greater than 99th percentile.

Acanthosis Nigricans

Neck and axilla of all fifth grade students were screened for this hyperpigmented skin rash associated with insulin resistance and hyperinsulinemia in children (17). Our screening staff was trained on the use of previously validated criteria (18), and was required to report whether AN was present or absent (*see* online supplement).

Fasting Lipid Profile

Blood samples for fasting lipid profile were obtained from fifth grade children only and were analyzed by LabCorp Inc. (Burlington, NC). A personalized report including serum levels of total cholesterol, LDL, HDL, and triglycerides was generated for each participant.

Study Protocol

CARDIAC screening procedures have been described in detail by previous publications (14, 15). In brief, this project screens more than 24,000 children annually in collaboration with the West Virginia Rural Health Educational Partnerships (WVRHEP). For each county, WVRHEP provides one site coordinator, one assistant coordinator, and health sciences students completing rural rotations at selected sites.

WVRHEP site coordinators and school teachers distributed consent booklets to all children enrolled in kindergarten, second grade, and fifth grade. Parents and legal guardians were asked to return the signed consent forms to their children's classroom teachers. In turn, the site coordinators collected the forms from the teachers before the scheduled screening date. Fifth grade students were screened at the beginning of screening day, because they were required to fast for the lipid profile blood draw and had to eat breakfast before going to class that morning. All information obtained from the screening was summarized in a comprehensive health report and mailed to the children's families. Each report also contained information on how to interpret the screening results, what additional services may be needed, and how to maintain a healthy lifestyle with adequate diet and physical activity.

Statistical Analysis

Complete statistical information is provided in the online supplement.

RESULTS

Sample Characteristics

We studied a sample of 17,944 children including 6,314 kindergarten students (35.2%); 5,609 second grade students (31.2%); and 6,021 fifth grade students (33.5%). Slightly less than half (49.3%) of these children were male (8,854 males vs. 9,027 females). Racial distribution of the sample was slightly more diverse than the total population of West Virginia, with 90.7% of children being white compared with 95.9% statewide. Most of the mothers (57.1%) had completed some college or obtained a college degree; 49.9% of fathers had obtained the same amount of education (Table 1).

Almost one third of the children's parents (30.2%) reported heart attacks among their first-degree relatives, and almost half reported surgical interventions for coronary disease (19.5% open heart surgery, 26.7% angioplasty). Approximately half of the sample (49.1%) reported a family history of diabetes. Also, approximately one (28.5%) out of four children had been exposed to second-hand tobacco smoke. Females were more likely to be underweight ($P < 0.001$), whereas males were more likely to be morbidly obese ($P < 0.001$). Males were also more likely to have been diagnosed with asthma ($P < 0.01$). We found no other relevant sex differences in demographic characteristics or family history.

Asthma Prevalence Based on Weight Category

The BMI percentile classification revealed that more than one-third of the children in our sample (37.6%) had a weight above healthy range, and one (20.9%) out of five children was obese or morbidly obese. Fourteen percent of the overall sample had been diagnosed with asthma by a medical provider according to their parents or legal guardians. Overall, asthma and BMI were found to be significantly correlated ($P = 0.02$). The percent of people with asthma within each BMI category of the total sample is illustrated in Figure 1. As a general trend, the asthma prevalence rate increased as children's BMI percentile increased. Importantly, asthma prevalence in children who were obese and morbidly obese was significantly higher than in children with healthy BMI ($P < 0.001$), whereas simple overweight status did not increase asthma risk ($P = 0.82$).

Figure 1 also illustrates asthma prevalence as it is distributed across grade and sex categories. Again, in most instances the

TABLE 1. SAMPLE CHARACTERISTICS

Characteristics (<i>n</i> = 17,944)	Number in Sample	% of Total Sample	Males (<i>n</i> = 8,854) %	Females (<i>n</i> = 9,027) %	Sex Difference <i>P</i> Value
Maternal education					
High school or fewer years	1,956	10.9	8.6	12.7	
High school graduate or GED	5,903	32.9	34.2	39.1	
Some college	5,903	32.9	40.0	40.0	
College graduate	4,163	23.2	16.7	17.1	
Paternal education					
High school or fewer years	4,001	22.3	24.0	21.1	
High school graduate or GED	5,132	28.6	28.0	28.9	
Some college	6,262	34.9	48.0	26.3	
College graduate	2,369	13.2	0.0	23.6	
Race or ethnicity					
White	16,201	90.7	49.7	50.3	
African American	408	2.3	50.2	49.8	
Asian	99	0.6	42.4	57.6	<0.05
Biracial	38	0.2	47.4	52.6	
Other	10	0.1	20.0	80.0	<0.01
Family history					
History of parent heart attack	5,398	30.2	49.8	50.2	
Heart surgery	3,481	19.5	49.2	50.8	
Angioplasty	4,762	26.7	49.5	50.5	
Diabetes	8,835	49.1	48.7	49.4	
Diagnosed with asthma	2,521	14.1	57.8	42.2	<0.01
Exposed to tobacco smoke	5,102	28.5	48.2	51.8	
Body mass index percentiles					
Underweight, <5th%	824	4.6	46.8	53.2	<0.001
Normal weight, 5th–84.9th%	9,965	55.8	48.8	51.2	
Overweight, 85th–94.9th%	2,981	16.7	49.7	50.3	
Obese, 95th–98.9th%	2,600	14.6	49.6	50.4	
Morbidly obese, ≥99th%	1,134	6.3	57.3	42.7	<0.001

Note: Not all cells within this table add up to 100% because of missing data (i.e., no response provided for the item).

prevalence of asthma was higher for higher BMI percentile categories. For example, 14.2% of male kindergarten students with healthy BMI had asthma compared with 22.2% of the kindergarten students who were morbidly obese male ($P < 0.01$), and this difference persisted into adolescence (14.9% vs. 26.4% in fifth grade; $P < 0.01$). Across grades, children who were obese and morbidly obese had consistently the highest percentages of asthma both for males and females ($P < 0.001$),

and children who were simply overweight were consistently similar to those with healthy weight. In contrast, asthma patterns for children who were underweight were more variable and differed for males and females and by grade.

Metabolic Variables Based on Weight Category

Table 2 and Figure 2A illustrate the mean serum levels for total cholesterol, LDL, HDL, and triglycerides distributed by

Figure 1. Asthma prevalence based on weight category. As a general trend, asthma prevalence increased as children's body mass index percentile increased. Asthma prevalence in children who are obese and morbidly obese was significantly higher than in children with healthy body mass index, whereas simple overweight status did not increase this risk. Asthma patterns in children who are obese were similar for males and females and across grades.

body weight category. In general, obesity was associated with significantly higher levels of total cholesterol, LDL, and log-transformed triglycerides, and with lower levels of HDL ($P < 0.0001$ for each analysis of variance model). However, whereas the serum levels of total cholesterol and LDL increased only slightly going from overweight to obese and actually decreased going from obese to morbidly obese, triglycerides increased progressively and significantly as the BMI category increased ($P < 0.001$ for each category) and a sharp increase was noted between the obese and morbidly obese categories. A pattern similar to that of serum triglycerides was noted for the prevalence of AN (Figure 2B).

Asthma Prevalence Based on Metabolic Variables

Because the serum triglyceride and AN profiles mimicked closely the trends of asthma prevalence in our sample, we tested the hypothesis that triglycerides (along with the rest of the fasting lipid panel) and AN are associated with the prevalence of childhood asthma independent of weight status. Figure 3 shows the proportion of fifth grade children with high serum levels for total cholesterol, LDL, HDL, and triglycerides (Figure 3A) and the proportion of fifth grade children with evidence of AN (Figure 3B) based on the presence or absence of asthma diagnosis. A statistically significant effect was found for the overall model of asthma diagnosis ($P = 0.016$). But more importantly, serum triglycerides (log-transformed; $P = 0.011$) and AN ($P = 0.006$) were significantly associated with asthma regardless of weight status and after controlling for sex and smoking status, thereby supporting our hypothesis.

In addition, we examined the association between overweight or obese weight status and serum lipids or AN, independent of the prevalence of asthma. The overall model was again significant ($P < 0.001$) for all dependent variables including total cholesterol, HDL, LDL, log-transformed triglycerides, and AN after controlling for sex and smoking status. Finally, we tested whether asthma diagnosis and BMI interact to affect serum lipids, but in this case we did not find a significant effect for the overall model ($P = 0.14$). Collectively, these results suggest a strong relationship between asthma diagnosis, serum triglycerides, and AN regardless of weight; a strong relationship between weight, serum lipids, and AN regardless of asthma diagnosis; and no interaction between BMI and asthma on serum lipids.

Relationships between Asthma and Metabolic Dysfunction

After discovering the general trends outlined previously, we explored individual relationships between asthma diagnosis and serum lipid levels by hierarchical linear regression (Figure 4A and Table 3). The overall model was significant (adjusted $R^2 = 0.07$; $P < 0.01$) and asthma was significantly associated with hypertriglyceridemia after controlling for sex, smoke exposure, and BMI percentile ($\Delta R^2 P = 0.006$). Similarly, we used binary logistic regression to explore the association between presence of AN and diagnosis of asthma (Figure 4B). The overall model was again significant (Nagelkerke $R^2 = 0.09$; $P < 0.001$) and

asthma was significantly associated with AN after controlling for sex, smoke exposure, and BMI percentile. Thus, the diagnosis of asthma continued to be significantly associated with both triglycerides levels and AN after controlling for sex, smoke exposure, and BMI.

DISCUSSION

The results of this study confirm that asthma prevalence generally increases with the children's BMI percentile. More specifically, asthma prevalence is increased among children who are obese, and even more so in children who are morbidly obese, although it is not more prevalent among children who are overweight compared with those of normal weight. This suggests that only above a certain threshold metabolic factors participate in the pathophysiology of airway inflammation and hyperreactivity, leading to the clinical manifestations of asthma and the use of health care resources culminating in the physician diagnosis of asthma. It is possible, however, that milder, subclinical abnormality in pulmonary function may already emerge in the overweight status. Our data also confirmed general age and sex differences in asthma prevalence, with older children and males being more affected.

To our knowledge, this is the first study to examine the association between physician-diagnosed asthma and weight using a large community-based sample of children with varying age, body mass, and metabolic risks. Our previous work has shown that about 50% of the eligible students participate in the CARDIAC screenings and that the differences between participants and nonparticipants are minimal (19). Nonparticipants are less likely to have a primary care provider and to have health insurance, but there is no difference in BMI or any other of the variables analyzed in the present study.

Furthermore, our data indicate that children diagnosed with asthma tend to have higher serum triglyceride levels based on age-specific reference values (20), and higher rates of insulin resistance as predicted by the AN biomarker. This association is independent of the children's sex and history of exposure to tobacco smoke. Most importantly, this association exists regardless of the children's body mass, implying that children whose weight is within or even below the healthy range may still be more susceptible to develop asthma because of subtle metabolic derangements heralded by increasing triglyceride or glucose blood levels. Also, it is possible that the reported association between obesity and asthma may have been confounded by the frequent association of obesity, hypertriglyceridemia, and insulin resistance.

Several previous studies have focused on childhood obesity to better understand the apparent clustering of chronic conditions, such as asthma, diabetes, and cardiovascular diseases (8, 21). In addition to the hypothetical relationship between obesity and asthma, there is strong evidence that obesity is associated with the development of insulin resistance and diabetes (22). In turn, diabetes and insulin resistance are associated with diminished lung function (23–25), and some studies have also

TABLE 2. MEAN SERUM LIPID VALUES BY BODY WEIGHT CATEGORY

Weight Category	TC	SEM	HDL	SEM	LDL	SEM	TRIG	SEM
Underweight BMI <5th%, n = 592	156.71	1.20	49.89	0.51	88.11	1.05	94.19	2.55
Healthy weight BMI 5th–84.9th%, n = 2,269	157.87	0.53	54.7	0.25	91.20	0.55	74.28	0.82
Overweight BMI 85th–94.9th%, n = 861	161.45	0.98	50.00	0.35	96.72	1.01	91.16	1.69
Obese BMI 95th–98.9th%, n = 905	165.21	0.99	45.32	0.33	100.69	0.99	118.14	2.16
Morbidly Obese BMI >99th%, n = 283	162.03	1.80	41.59	0.55	98.16	1.88	133.54	4.92

Definition of abbreviations: BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TRIG = triglycerides.

Figure 2. Metabolic variables based on weight category. Mean serum levels for total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TRIG) (A) and prevalence of acanthosis nigricans (AN) (B) distributed by body mass index percentile. Whereas the serum levels for TC and LDL increased only slightly going from overweight to obese, and actually decreased going from obese to morbidly obese, serum TRIG and AN prevalence increased progressively and significantly as the body mass index category increased.

found a relationship between insulin resistance and reduced lung function among nondiabetics, even after controlling for BMI (23, 26).

Based on the present data, we have formulated the hypothesis that early metabolic abnormalities induced by imbalanced diet during pregnancy and childhood constitute the central hub from which the asthma-obesity-diabetes triad originates, at least in a subpopulation of patients. To test this hypothesis, we have recently developed in parallel to our epidemiologic studies an animal model of the effects of hypercaloric diet on metabolic

and airway responses in rats. Our initial data show that dietary imbalances during pregnancy and lactation are associated with inflammation and airway hyperreactivity early in life (27), suggesting a role for maternal diet as a risk factor for the development of childhood asthma. Interestingly, the primary metabolic abnormality found in the hyperreactive offspring from dams fed with high-fat diet was hypertriglyceridemia, which correlated with body fat but not with body weight (27).

The information provided by this study also confirms the disproportionate burden of environmental and metabolic risk

Figure 3. Metabolic variables based on asthma status. Proportion of children with dyslipidemia according to age-specific reference values (20) for total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TRIG) (A), and proportion of children with evidence of acanthosis nigricans (AN) (B) based on the presence or absence of asthma diagnosis. Serum TRIG and AN were found to be independently associated with asthma regardless of weight status and after controlling for sex and smoking status.

Figure 4. Relationships between asthma and metabolic dysfunction. Hierarchical linear regression model predicting serum triglyceride levels (A) and binary logistic regression predicting the presence of acanthosis nigricans (AN) (B) based on the diagnosis of asthma. Asthma diagnosis continued to be significantly associated with both hypertriglyceridemia and AN after controlling for sex, smoke exposure, and body mass index (BMI) percentile.

factors in the low-income, predominantly rural populations of West Virginia and Appalachia, which makes these populations uniquely suited for studies of the pathogenesis of chronic diseases. In particular, the prevalence of cardiovascular risk factors and diabetes found in the families included in our sample is consistent with the most recent statewide epidemiologic data (complete information on the burden of diabetes in West Virginia is provided in the online supplement) and is higher than the national average (28, 29). The prevalence of tobacco smoke exposure in the home (28.5%) is also above the national average of approximately 25%. Finally, the incidence of obesity (20.9%) is higher than the national estimate based on the 2003–2006 National Health and Nutrition Examination Survey that 17% of children 6 to 11 years old and 17.6% of children 12 to 19 years old are obese or morbidly obese in the United States.

It should be noted that, although a few towns with higher population qualify as urban areas, most of the 55 counties within the state of West Virginia have been characterized as rural locations by multiple sources (complete information on rural definitions and distribution of rural areas in West Virginia is provided in the online supplement).

TABLE 3. REGRESSION ANALYSIS PREDICTING METABOLIC DYSFUNCTION BASED ON ASTHMA DIAGNOSIS

Dependent Variable	Independent Variable	β	P Value	Adjusted R^2	ΔR^2 P
Serum triglycerides	Sex	0.10	0.0001	0.066	
	Smoke	0.06	0.0001		
	BMI%	0.23	0.0001		
	Asthma	0.04	0.006	0.067	0.006
Dependent Variable	Independent Variable	β	P	Nagelkerke R^2	OR
<i>Acanthosis nigricans</i>	Sex	0.22	0.060	0.091	1.24
	Smoke	0.47	0.0001		1.61
	BMI%	0.03	0.0001		1.03
	Asthma	0.32	0.023	0.093	1.38

Definition of abbreviations: BMI = body mass index; OR = odds ratio.

Asthma and Triglycerides

A number of pathophysiologic mechanisms could explain the direct association found in our study between childhood asthma and high serum triglycerides. In particular, this association is consistent with the hypothesis that both pathologic entities result from the changing diet patterns of today's children, regardless of their body mass. For example, children are consuming smaller amounts of antioxidants, which have been shown to protect against asthma (30–32), and have increased their dietary fat intake, which contributes to high serum triglyceride levels (33, 34).

Inflammation is another mechanism by which metabolic abnormalities may promote the development of asthma. Multiple cytokines (e.g., tumor necrosis factor- α , IL-1, IL-6), hormones (e.g., leptin, adiponectin), and acute-phase reactants (e.g., C-reactive protein) participate to both metabolic and inflammatory pathways and are overexpressed in both asthma and obesity resulting in a chronic, low-grade inflammatory state that also promotes insulin resistance (33, 34). However, the limited number of studies that investigated the link between obesity and airway inflammation in children by exhaled nitric oxide (35, 36) or breath condensate (37) were unable to find any association.

Potential limitations of this study include the reliability of parents' reports of physician-diagnosed asthma and mandate the use of objective measurements of pulmonary function in future studies. However, spirometry is logistically impossible in the context of a community-based screening program using a sample of this size, and therefore these follow-up studies will necessarily involve much smaller cohorts. Also, most children diagnosed with asthma have normal pulmonary function at baseline, and their diagnosis is based solely on historical and clinical data. Another potential issue is the predominantly rural nature of the sample, which may be affected by environmental exposures less usual in urban areas (e.g., coal and wood stoves) and may play a part in the higher prevalence of asthma compared with the national average (38). On the other hand, our findings are surprising considering the predominant exposure of our sample to a farming environment, and argue strongly against the basic principles of the "hygiene hypothesis," or at least suggest that nutritional and metabolic factors can override the protective effect of farming.

Asthma and Diabetes

Increasing rates of pediatric asthma could also result directly from peripheral tissue insulin resistance and compensatory hyperinsulinemia, which may interfere with the antiinflamma-

tory effects of insulin while increasing bronchial reactivity through inhibition of presynaptic M2 muscarinic receptors (39). In addition, intracellular serine/threonine kinases, such as c-Jun NH(2)-terminal protein kinases, are activated by Toll-like receptor signaling in the context of innate immunoinflammatory responses, and also inhibit insulin signaling (38). Because of the close interdependence between inflammatory and metabolic pathways emerging from this study, pharmacologic ligands of the peroxisome proliferator-activated family of nuclear receptor proteins widely used to treat hyperlipidemia and diabetes may also improve the airway inflammation and hyperreactivity characteristic of asthma.

Of course, our data cannot elucidate the chronologic sequence of events linking hypertriglyceridemia, insulin resistance, and the inflammation seen in obesity and asthma. For example, it is impossible to rule out that airway inflammation is the primary event leading to secondary hypertriglyceridemia and insulin resistance. Therefore, additional studies are needed to explore the complex interactions among the multiple pathways involved in this association and creating increased vulnerability among children. Also, individual differences in pubertal stage may have an influence on some of the study variables, such as insulin resistance, and have to be reassessed in future studies.

Finally, potential error may derive from using AN as a proxy for insulin resistance because, although AN is highly predictive of insulin resistance in adults, its significance in children is less documented and some studies have questioned its predictive value (40, 41). However, a recent analysis of CARDIAC data (42) has shown that 60.8% of children with AN have an abnormal (i.e., ≥ 3) homeostatic model assessment index of insulin resistance and β -cell function based on fasting plasma glucose and insulin concentrations (43), and other previous studies have shown that children with AN are 1.6 to 4.2 times as likely as their counterparts without AN to have hyperinsulinemia (44, 45). Thus, although this biomarker is less than optimal, it is without doubt associated with insulin resistance and the highly significant relationship between asthma and AN among this large and diverse sample of children warrants further studies to better understand the pathophysiologic link between insulin resistance and asthma in children, which has been confirmed very recently in another small study based on homeostatic model assessment (46).

In conclusion, this study is the first analysis of the relationship between asthma and body mass in a large and diverse sample of school-age children across the entire range of weight percentile categories, and shows that children with physician-diagnosed asthma tend to have higher serum triglyceride levels and higher rates of insulin resistance as predicted by the AN biomarker, regardless of the children's body mass. Thus, dyslipidemia and hyperinsulinemia, known silent precursors to cardiovascular disease and diabetes, may also be associated with the development of asthma and confound its epidemiologic link to obesity. Our findings imply a strong and direct influence of metabolic pathways on the immune mechanisms, both innate and adaptive, involved in the pathogenesis of asthma in children, and suggest that strict monitoring and dietary and pharmacologic control of triglyceride and glucose levels starting in the first years of life may have a critical role in the management of chronic asthma in children.

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