Exploring the Relationship Between Childhood Obesity, Asthma, and Metabolic Disease

LESLEY COTTRELL, PHD

WEST VIRGINIA UNIVERSITY, SCHOOL OF MEDICINE, DEPARTMENT OF PEDIATRICS

Why Childhood Obesity, Asthma, and MetabolicDisease?

- Significant health issues for state and nation
  - National prevalence among children (7 million children under 18 years; 9%)
  - West Virginia prevalence among children (43,465 children; 14.7%)
- Parallel rise in childhood obesity and asthma rates
  - Asthma prevalence has doubled among children in the last two decades
  - Obesity prevalence has tripled among children in the last two decades
- Similar patterns
  - Both are more prevalent among younger boys but become greater among girls in adolescence

Associations

- **Obesity and asthma are related**
  - Asthmatics are more likely to become overweight/obese over time
  - Obese children are more likely to develop asthmatic symptoms
    - Obese children are less effected by select asthmatic treatments
- **Which comes first?**
  - Obesity is central but which comes first in most instances is unknown
- **How is obesity, asthma, and metabolic disease related?**
  - Obesity as central hub - these illness are related to dyslipidemia, cardiovascular risk factors

Literature Gaps

- How are asthma, obesity, and metabolic function associated with one another across a spectrum of children?
  - Most studies are conducted using obese child samples or only asthmatics
- Is childhood obesity always the central support for the triad, if it exists?
  - Studies prior to our project did not control for obesity in analyses. It was always included as an independent variable of models
- Are there developmental differences associated with puberty and other physiological milestones that should be considered?
  - Most studies have used adolescent or young adult samples

Initial Research Questions

- Phase I Project
  - Examine the relationship between asthma and body mass in children in a wide spectrum sample
  - Test whether early derangement in lipid and glucose metabolism is independently associated with increased risk for asthma

Metabolic Abnormalities in Children with Asthma

Lesley Cottrell[1], William A. Neal[1], Christa Ice[1], Miriam K. Perez[1], and Giovanni Piedimonte[1]

[1]Department of Pediatrics and Pediatric Research Institute, West Virginia University School of Medicine, Morgantown, West Virginia

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

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.

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 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 (8); 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 anti-inflammatory 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-

(Received in original form April 17, 2010; accepted in final form September 16, 2010)

Supported in part by a grant from the US National Institutes of Health (NICHD NCS-07-11). The screening design and procedures were funded by the West Virginia Bureau of Public Health and the Claude W. Benedum Foundation. Dr. Giovanni Piedimonte was also funded in part by grant NHLBI HL-67087 and funds from the WVU Foundation.

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).

Correspondence and requests for reprints should be addressed to Giovanni Piedimonte, M.D., Department of Pediatrics, West Virginia University School of Medicine, Robert C. Byrd Health Sciences Center, 1 Medical Center Drive, P.O. Box 9214, Morgantown, WV 26506-9214. E-mail: gpiedimonte@hsc.wvu.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 183. pp 441–448, 2011
Originally Published in Press as DOI: 10.1164/rccm.201004-0601OC on September 17, 2010
Internet address: www.atsjournals.org

Phase I Participants

- CARDIAC Participants from 2007-2008 academic year (n = 17,944)
  - kindergarten (4-5 years) - n = 6,314
  - second grade (7-8 years) - n = 5,609
  - fifth grade (9-10 years) - n = 6,021
- 49.3% males
- 90.7% Caucasian
- Parental consent and child assent

Phase I Measures

- **Childhood Obesity**
  - Body mass index percentile (BMI%)
    - SECA Road Rod stadiometer
    - SECA 840 Digital Scale
  - Categorical Variable
    - < 5th% - underweight
    - 5th-84.9th% - healthy weight
    - 85.0-94.9th% - overweight
    - 95.0-98.9th% -obese
    - ≥ 99th% - morbidly obese

Phase I Measures

- **Metabolic Disease**
  - Acanthosis Nigricans (AN)
    - Neck and axilla hyperpigmented skin rash
    - Associated with insulin resistance and hyperinsulinemia in children (Hud, Cohen, Wagner, Cruz; 1992)
  - Dichotomous Variable
    - Present/Absent

Phase I Measures

- **Childhood Asthma**
  - Single item for parent report
    - "Has your child been diagnosed with asthma"
    - Yes/no response
- **Lipids**
  - Fifth grade students only
  - Total cholesterol, LDL, HDL, Triglycerides

Asthma Prevalence Based on BMI

- 37.6% were overweight or above
- 1 in 5 children were obese or morbidly obese
- 14% had been diagnoses with asthma
- General trend: asthma prevalence rate increased as BMI% increased
- Significantly more obese/morbidly obese children were asthmatic than healthy weight children ($p<.001$) across grades

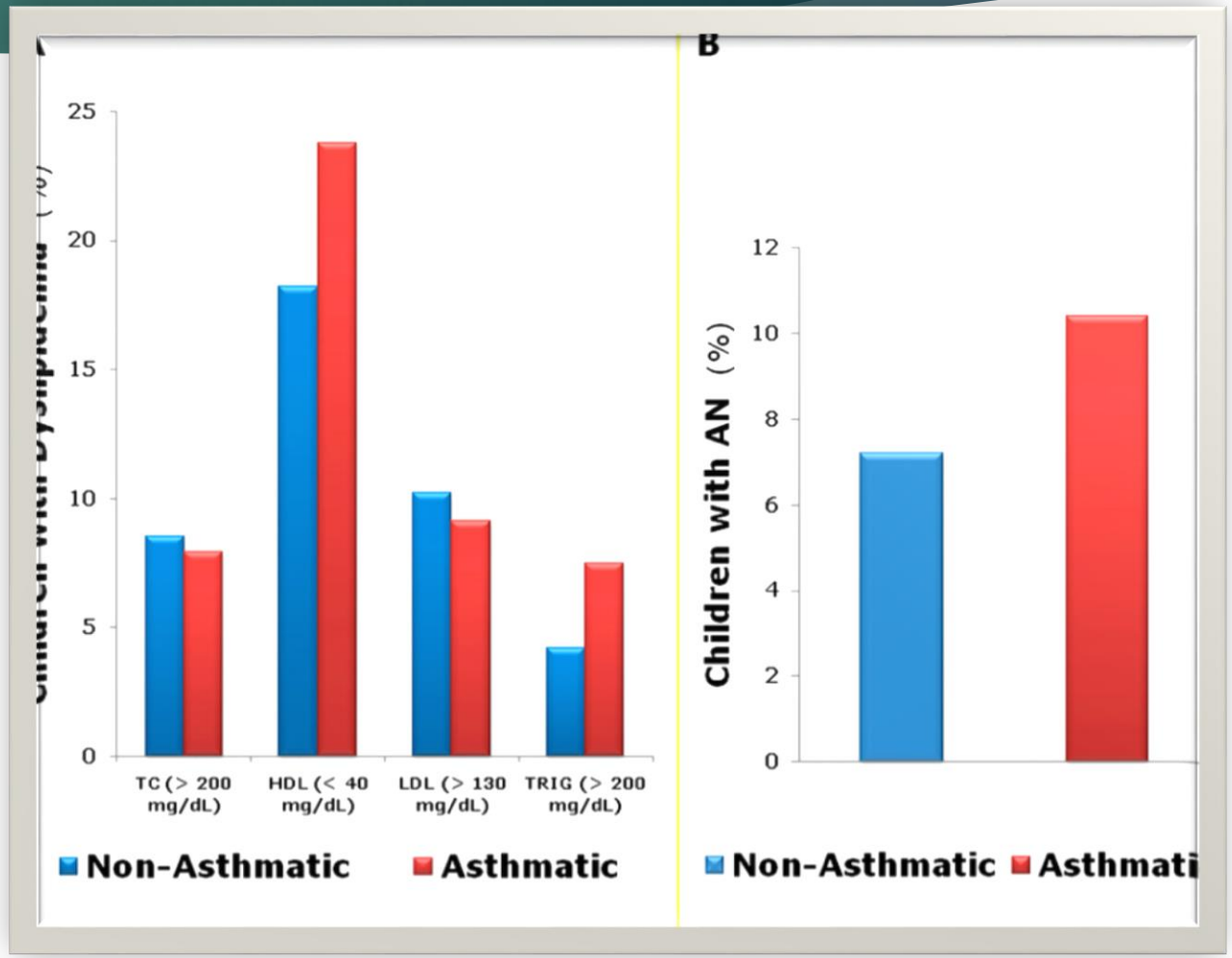
Metabolic Variables Based on BMI

- Obesity was associated with:
  - higher means of total cholesterol, LDL and log-transformed triglycerides
  - lower means of HDL
- Presence of AN was associated with:
  - higher means of triglyercides

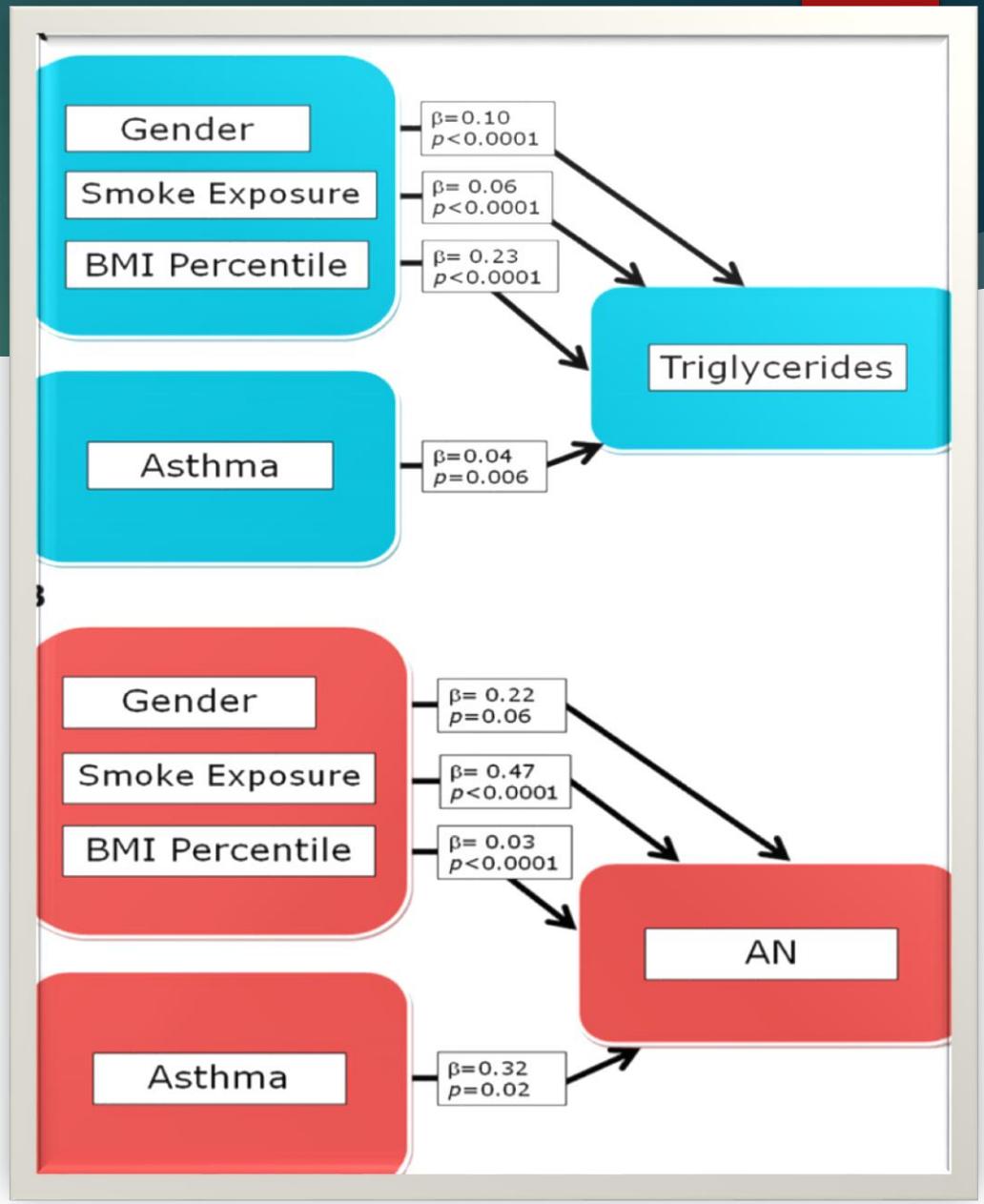
Independence from Obesity

- Significant asthmatic effect (p<.01)
- Significant associations between asthma and:
  - triglycerides (p<.01)
  - AN (p<.001)

  - regardless of weight status
  - controlling for sex and smoke exposure



- Hierarchical linear regressions illustrated that:
  - asthma associated with hypertriglyceridemia after controls (p<.01)
  - asthma associated with AN after controls (p<.001)



Phase I: Summary Points and Limitations

- **Summary Points**
  - Additional evidence of obesity and asthmatic burden in WV among children
  - Provides initial evidence for an alternative model without obesity as the central hub but rather, diet as the initiator of asthma-obesity-diabetes triad

- **Limitations**
  - "Indirect" assessments/ variables
  - Cross-sectional design
  - Limited lipid analyses

What Does this Mean?

- Metabolic abnormalities induced by imbalanced diet in childhood may constitute central hub of asthma-obesity-diabetes triad
- Possibly different type of asthma and metabolic abnormalities that are linked directly to asthma without obesity as central structure
- What is the mechanism?
  - Inflammation?

Phase II: The Family Lifestyle Project

- Designed to…:
  - replicate Phase I analyses with direct, clinical assessments of model variables;
  - continue to assess obesity-asthma-metabolic abnormality triad across spectrum of children; and
  - explore potential mechanisms supporting asthma-metabolic abnormality association independent of, obesity

Phase II: Assessments

- **Blood Samples** (15 cc total)
  - Lipids, glucose, insulin, IgE, Vitamin D, Hemoglobin
  - Serum nitrate/nitrite
  - GWAS
  - Cytokines, NGF, BDNF
  - Store serum for future questions
- **Urine Sample**
  - Nicotine and cotinine

- **Clinical Assessments**
  - PFTs
  - Exhaled Breathe Condensate (EBC)
  - Anthropometrics& DEXA
  - History and Physical
  - Allergy Testing
- **Surveys**
  - Demographics
  - Child Health Questionnaire
  - Parental Stress Index
  - Sleep Questionnaire
  - Physical Activity & Diet
  - Executive Function
  - Asthma Control

Phase II: Procedures

- **Prior to Visit**
  - Discontinue medication and fast overnight (at least 12 hours before visit)
  - Complete series of surveys
- **During Visit**
  - Check-in, anthropometrics, fasting blood draw, urine collection
  - DEXA
  - History & Physical
  - PFTs, EBC
  - Allergy Testing
- **After Visit**
  - Health report mailed to family
  - Health literacy survey

Phase II Participants

- 178 children
  - 56.8% males
  - 85.4% Caucasian
  - Positive family hx for diabetes = 42.4%
  - Child diagnosed with diabetes = 1.1%

  - Mean age = 9.4 years (SD = 1.7)
    - 7-13 years of age included
  - Mean BMI% = 67.6 (SD= 30.2)
    - 2.9% underweight
    - 53.5% healthy weight
    - 16.9% overweight
    - 18.6% obese
    - 8.1% morbidly obese

Asthma Prevalence

- **Confirmation Method**
  - medications
  - PFT
  - prior history
  - physical & history

- **Asthma Prevalence in Sample**
  - 102 (57.3%) non-asthmatic
  - 76 (42.7%) asthmatic
  - 36.8% of females; 45.4% of males
  - 42.8% of 7-9 year-olds; 39.0% of 10-12 year-olds

Lipid and Metabolic Abnormalities

- **% abnormal - fasting lipids**
  - 4.5% Total cholesterol (cut off value = 200 mg/dL)
  - 2.1% LDL (cut off value = 190 mg/dL)
  - 10.1% HDL (cut off value = 39 mg/dL0
  - 2.9% Triglycerides (cut off value = 200 mg/dL)

- **% abnormal - metabolic function**
  - 1.2% HOMA IR (cut off value = 5.22 in boys; 3.82 in girls; Kurtoglu et al., 2010)
  - 0.6% HbA1C (cut off value = 6.5%; WHO report; 2011)

Asthma and Obesity Association

- 3.1% underweight
- 18.0% healthy weight
- 9.0% overweight
- 9.0% obese
- 3.9% morbidly obese

- Significant association between variables ($p<.01$); non-linear

Obesity, Lipids, and Metabolic Function

- Greater BMI% was significantly associated with:
  - higher triglycerides ($p<.01$)
  - lower HDL ($p<.001$)
  - higher LDL ($p<.001$)
  - higher insulin ($p<.001$)
  - higher HOMA-IR ($p<.001$)

- **Note: association with abnormal HbA1c but NS**

Asthma, Lipids, and Metabolic Function

- Asthmatics were significantly more likely to have:
  - elevated triglycerides ($p<.05$)
  - hyperinsulinemia ($p<.01$)
  - abnormal HOMA-IR ($p<.01$)

Still Independent of Obesity?

- Hierarchical linear regressions controlling for age, gender, and obesity significantly predicted:
  - Triglycerides ($p<.05$)
  - Insulin ($p<.05$)
  - HOMA-IR, HbA1C - not significant

Phase II: Summary Points and Limitations

Summary Points

- Partial replication of the original question using clinical and direct assessments was supported
- Asthma may be directly related to metabolic abnormalities, perhaps through diet but this is not consistent across measures

Limitations

- Despite recruitment strategies, sample includes fewer obese/asthmatics
- Some cut offs are not confirmed for children in literature at this time

Next Steps

- Conduct ROC analyses using different cut offs for metabolic assessments
- Explore inflammatory markers and other variables to begin to detangle differences in metabolic measures
- Explore fatty acids and other nutritional indices from serum to look potential role of diet on triad
- Use DEXA (on subsample only) instead of BMI% to assess model

Lab Members

WVU

Brian Ansell
Rafka Chaiban
Brad Foringer
Michael McCawley
William Neal
Jan Rapp
Christa Lilly
Talia Sotomayor
Sylvia Cardenas
Yemir Demirdag
Stephanie Grayson
Hawley Montgomery
Ali Onder
Michael Regier
Lennie Samsell
Cheryl Walton

Other Institutions

Greg Hawkins (Wake Forest)
Adam Gower (Wake Forest)
Srinivas Nagaraj (U of Florida)

References

- CDC. Asthma in West Virginia. Accessed at: www.cdc.gov/asthma/stateprofiles/asthma_in_WV.pdf
- CDC. Asthma Surveillance Data. Accessed at: www.cdc.gov/asthma/asthmadata.htm
- Ogden, Carroll, Kit, Flegal. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA 2012; 307: 483-490.
- Borrell et al., Childhood obesity and asthma control in the GALA II and SAGE II studies. Am J Respir Crit Care Med 2013; 187 (7): 697-702.
- Matricardi, Gruber, Wahn, Lau. The asthma-obesity link in childhood: open questions, complex evidence, a few answers only. Clin Exp Allergy 2007; 37: 476-484.
- Cottrell, Neal, Ice, Perez, Piedimonte. Metabolic abnormalities in children with asthma. Am J Respir Crit Care Med 2011; 183: 441-448.
- Hersoug, Linneberg. The link between the epidemics of obesity and allergic diseases: Does obesity induce decreased immune tolerance? Allergy 2007; 62: 1205-1213.
- Farah, Kermode, Downie, Brown, Hardaker, et al. Obesity is a determinant of asthma control independent of inflammation and lung mechanics. Chest 2011; 140: 659-666.