Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma

Erick Forno, MD, MPH,[a]* Yueh-Ying Han, PhD,[a]* Radhika H. Muzumdar, MD,[b] and Juan C. Celedón, MD, DrPH[a]

Pittsburgh, Pa

Background: Obesity increases both the risk of asthma and asthma severity and is a well-known risk factor for insulin resistance and the metabolic syndrome (MS) in children and adolescents.

Objective: We aimed to examine the association among obesity, insulin sensitivity, MS, and lung function in US adolescents with and without asthma.

Methods: We performed a cross-sectional study of 1429 adolescents aged 12 to 17 years in the 2007-2010 National Health and Nutrition Examination Survey. Adjusted regression was used to assess the relationships among obesity, insulin sensitivity/resistance, MS, and lung function in children with and without asthma.

Results: Insulin resistance was negatively associated with FEV_1 and forced vital capacity (FVC) in adolescents with and without asthma, whereas MS was associated with lower FEV_1/FVC ratios, with a more pronounced decrease found among asthmatic patients; these associations were driven by overweight/obese adolescents. Higher body mass index was associated with a decrease in FEV_1/FVC ratios among adolescents with insulin resistance. Compared with healthy participants, adolescents with MS had an approximately 2% decrease in FEV_1/FVC ratios, adolescents with asthma had an approximately 6% decrease, and those with MS and asthma had approximately 10% decreased FEV_1/FVC ratios ($P < .05$).

Conclusion: Insulin resistance and MS are associated with worsened lung function in overweight/obese adolescents. Asthma and MS synergistically decrease lung function, as do obesity and insulin resistance. These factors might contribute to the pathogenesis of asthma severity in obese patients and warrant further investigation. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, lung function, insulin resistance, adiposity, obesity, metabolic syndrome, National Health and Nutrition Examination Survey*

Asthma and obesity are major public health issues in industrialized countries, such as the United States, with parallel increases in the prevalence of both diseases over the last few decades.[1-4] Epidemiologic studies have shown that childhood obesity is associated with increased risk of incident asthma, increased asthma severity and morbidity, and decreased response to long-term asthma medications.[5-8]

Childhood obesity is a known risk factor for insulin resistance, diabetes, and the metabolic syndrome (MS).[9,10] There is growing evidence that metabolic derangements, such as hyperglycemia and hyperinsulinemia, can lead to airway dysfunction and increased airway responsiveness through several pathways, including epithelial damage and airway smooth muscle proliferation.[11] A recent population-based study reported higher rates of acanthosis nigricans (a marker of insulin resistance) in children with asthma than in those without asthma, regardless of body mass index (BMI).[12] Conversely, morbidly obese children and adolescents with asthma have a higher incidence of insulin resistance than morbidly obese children and adolescents without asthma.[13,14] The MS has also been significantly associated with lung function impairment and asthma-like symptoms, with abdominal obesity being the key determinant of this association.[15,16]

We hypothesized that measures of insulin sensitivity (fasting glucose/insulin [G/I] ratio and the quantitative insulin sensitivity check index [QUICKI]) and insulin resistance (homeostasis model assessment-estimated insulin resistance [HOMA-IR]) are associated with lung function in adolescents, particularly among those with obesity or increased adiposity. We further hypothesized that the MS is associated with worse lung function and that detrimental effects of insulin resistance and MS on lung function are more pronounced in adolescents with asthma. We examined these hypotheses in a cross-sectional study of adolescents living in the United States.

METHODS

Subject recruitment

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional nationwide survey designed to assess the health and nutritional status of the noninstitutionalized population of the United States.[17] NHANES combines interviews and physical examinations of participants by highly trained personnel. Participants for the study are selected by using a stratified multistage probability design and are thus a representative sample of the US population. By design, ethnic minorities (African Americans and Mexican Americans) are oversampled to increase the statistical power for data analysis in these groups. Adolescents 12 to 17 years of age who participated in the 2007-2008 and 2009-2010 NHANESs were included in this analysis. Current

From [a]the Division of Pediatric Pulmonary Medicine, Allergy, and Immunology and [b]the Division of Pediatric Endocrinology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine.

*These authors contributed equally to this work.

E.F.'s contribution was supported by National Institute of Health (NIH) grant HD052892. J.C.C.'s contribution was supported by NIH grants HL079966 and HL117191 and by an endowment from the Heinz Foundation.

Disclosure of potential conflict of interest: J. C. Celedón's contribution was supported by grants HL079966 and HL117191 from the National Institutes of Health (NIH) and by an endowment from the Heinz Foundation. E. Forno's contribution was supported by grant HD052892 from the NIH. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 15, 2014; revised January 13, 2015; accepted for publication January 21, 2015.

Corresponding author: Erick Forno, MD, MPH, Division of Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Pittsburgh, PA 15224. E-mail: erick.forno@chp.edu.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.01.010

Abbreviations used
BMI: Body mass index
CRP: C-reactive protein
FVC: Forced vital capacity
G/I: Glucose/insulin
HDL: High-density lipoprotein
HOMA-IR: Homeostasis model assessment-estimated insulin resistance
MS: Metabolic syndrome
NHANES: National Health and Nutrition Examination Survey
PBF: Percentage body fat
QUICKI: Quantitative insulin sensitivity check index
WC: Waist circumference
WHtR: Waist/height ratio

asthma was defined as both having had asthma diagnosed by a doctor or other health care professional and at least 1 asthma attack in the past year. Participants who had neither diagnosed asthma nor an asthma attack in the past year were selected as control subjects. Participants who reported a lifetime diagnosis of asthma but no asthma attacks in the past year were excluded from this analysis. NHANES was approved by the Institutional Review Board of the National Center for Health Statistics of the US Centers for Disease Control and Prevention. Informed consent was obtained from all participants.

Study procedures

Measures of obesity and adiposity were collected by trained health technicians, according to recommendations from the *Anthropometric standardization reference manual*.[18] BMI was calculated as weight (in kilograms) divided by height (in meters squared). Percentage body fat (PBF) was calculated from tricipital and subscapular skin folds. For data analysis, all measures were transformed to z scores to obtain standardized and comparable coefficients: BMI z scores were calculated by using equations based on the 2000 US Centers for Disease Control and Prevention growth charts,[19] PBF z scores were calculated by using reference equations for US children,[20] and waist circumference (WC) and waist/height ratio (WHtR) values were standardized by using the distribution of these measures in our study population. Overweight/obese was defined as a z score of greater than 1.0364 (85th percentile) for each adiposity indicator.

Fasting plasma glucose, serum insulin, high-density lipoprotein (HDL) cholesterol, triglyceride, and C-reactive protein (CRP) levels were measured at a morning examination session in all NHANES participants aged 12 years and older. Participants fasting for less than 9 hours, taking insulin or oral medications for diabetes, or refusing phlebotomy were excluded. Insulin sensitivity was measured by using 2 indicators: fasting glucose (in microunits per milliliter)/insulin (in milligrams per deciliter [G/I]) ratio and QUICKI value. The QUICKI value was defined as follows:

$$1/\log[\text{Fasting insulin}]+\log[\text{Fasting glucose}].$$ [21]

Conversely, the HOMA-IR value was used as a measure of insulin resistance and was defined as follows:

$$(\text{Fasting insulin} \times \text{Fasting glucose}[\text{mmol/L}])/22.5.$$ [22]

Systolic blood pressure was measured in all NHANES participants according to study protocols[23] and was standardized for this analysis by using its distribution in our study population. MS was defined as meeting at least 3 of the following 5 criteria: fasting glucose level of 110 mg/dL or greater, WC value of the 75th percentile or greater, fasting triglyceride level of 100 mg/dL or greater, HDL level of 50 mg/dL or less, and systolic blood pressure of the 90th percentile or greater.[14,24]

Spirometry was performed according to American Thoracic Society recommendations.[25] The best FEV_1 and forced vital capacity (FVC) values were selected for data analysis. Participants were not eligible for spirometry if they were receiving supplemental oxygen or had painful ear infections, current chest pain or a physical problem with forceful expiration, recent surgery (of the eye, chest, or abdomen), heart disease, or tuberculosis. Our main analyses were performed by using absolute values (in milliliters) adjusted for age, sex, height, and height squared; confirmatory analyses were performed with NHANES III predictive equations for lung function measures and are included in this article's Online Repository at www.jacionline.org.

Statistical analysis

Primary sampling units and strata for the complex design of NHANES were taken into account for data analysis. Sampling weights, stratification, and clusters provided in the NHANES data set were incorporated into the analysis to obtain proper estimates and SEs; fasting sample weights were also used when analyzing fasting glucose and insulin levels. All multivariate analyses were performed with linear regression within the SURVEY procedure in SAS software (SAS Institute, Cary, NC). All models were adjusted for age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), family history of asthma, health insurance coverage, environmental tobacco smoke exposure, CRP level, and number of fasting hours; models for FEV_1 and FVC were additionally adjusted for height and height squared. In a secondary multivariate analysis we examined the relation between FEV_1/FVC ratios and overweight/obesity (BMI ≥85th percentile for age and sex) after stratification by asthma and MS. All statistical analyses were conducted with SAS 9.3 software.

RESULTS

The main characteristics of the 1429 participating adolescents with and without current asthma are shown in Table I (see Fig E1 in this article's Online Repository at www.jacionline.org for derivation of the study sample from NHANES). Compared with adolescents without asthma, those with asthma were more likely to be black and to have a low annual household income, health insurance, a family history of asthma, lower FEV_1, and lower FEV_1/FVC ratios ($P < .05$ in all instances). Adolescents with asthma also had a nonsignificant trend toward higher adiposity z scores than their nonasthmatic counterparts ($P < .10$). There were no statistically significant differences in age, sex, environmental tobacco smoke exposure, CRP levels, or indicators of MS or insulin resistance between adolescents with and without asthma. Similar results were found when comparing adolescents with "ever asthma" with healthy control subjects (see Table E1 in this article's Online Repository at www.jacionline.org).

Table II shows the results of the multivariate analysis of the relation between indicators of insulin sensitivity or resistance and lung function measures among all subjects and after stratification by asthma status. In this analysis greater insulin sensitivity (defined by higher G/I ratios or QUICKI values) was significantly associated with higher FEV_1 and FVC values in all subjects. Among subjects without asthma, each unit increment in G/I ratio was significantly associated with approximately 11- to 13-mL increments in FEV_1 and FVC values, respectively, and each 0.01-point increment in QUICKI value was significantly associated with approximately 24- to 30-mL increments in FEV_1 and FVC values, respectively. Among adolescents with asthma, these findings were more pronounced: significant increments of approximately 20 mL in FEV_1 and approximately 45 mL in FVC per each unit increment in G/I ratio and significant increments of approximately 42 mL in FEV_1 and approximately 59 mL in FVC per each unit increment in QUICKI value. Conversely, insulin resistance (defined by higher HOMA-IR values) was associated with lower FEV_1 and FVC values: each unit increase in HOMA-IR