Overweight/obesity status in preschool children associates with worse asthma but robust improvement on inhaled corticosteroids

Jason E. Lang, MD, MPH,[a] Anne M. Fitzpatrick, PhD,[b] David T. Mauger, PhD,[c] Theresa W. Guilbert, MD,[e] Daniel J. Jackson, MD,[f] Robert F. Lemanske, Jr, MD,[g] Fernando D. Martinez, MD,[h] Robert C. Strunk, MD,[i]† Robert S. Zeiger, MD, PhD,[j] Wanda Phipatanakul, MD, MS,[l] Leonard B. Bacharier, MD,[i] Jacqueline A. Pongracic, MD,[m] Fernando Holguin, MD,[d] Michael D. Cabana, MD,[k] Ronina A. Covar, MD,[n] Hengameh H. Raissy, PharmD,[p] Monica Tang, MD,[a] and Stanley J. Szefler, MD, PhD,[o] for the National Institutes of Health/National Heart, Lung and Blood Institute AsthmaNet *Durham, NC; Atlanta, Ga; Hershey and Pittsburgh, Pa; Cincinnati, Ohio; Madison, Wis; Tuscon, Ariz; St Louis, Mo; San Diego and San Francisco, Calif; Boston, Mass; Chicago, Ill; Denver and Aurora, Colo; and Albuquerque, NM*

Background: Overweight/obesity (OW) is linked to worse asthma and poorer inhaled corticosteroid (ICS) response in older children and adults.

Objective: We sought to describe the relationships between OW and asthma severity and response to ICS in preschool children.

Methods: This *post hoc* study of 3 large multicenter trials involving 2- to 5-year-old children compared annualized asthma symptom days and exacerbations among normal weight (NW) (body mass index: 10th-84th percentiles) versus OW (body mass index: ≥85th percentile) participants. Participants had been randomized to daily ICS, intermittent ICS, or daily placebo. Simple and multivariable linear regression was used to compare body mass index groups.

Results: Within the group not treated with a daily controller, OW children had more asthma symptom days (90.7 vs 53.2, $P = .020$) and exacerbations (1.4 vs 0.8, $P = .009$) thanNW children did. Within the ICS-treated groups, OW and NW children had similar asthma symptom days (daily ICS: 47.2 vs 44.0 days, $P = .44$; short-term ICS: 61.8 vs 52.9 days, $P = .46$; as-needed ICS: 53.3 vs 47.3 days, $P = .53$), and similar exacerbations (daily ICS: 0.6 vs 0.8, $P = .10$; short-term ICS: 1.1 vs 0.8 days, $P = .25$; as-needed ICS: 1.0 vs 1.1, $P = .72$). Compared with placebo, daily ICS in OW led to fewer annualized asthma symptom days (90.7 vs 41.2, $P = .004$) and exacerbations (1.4 vs 0.6, $P = .006$), while similar protective ICS effects were less apparent among NW.

From [a]the Department of Pediatrics, Duke University School of Medicine, Durham; [b]the Department of Pediatrics, Emory University, Atlanta; [c]the Department of Public Health Sciences, College of Medicine, Penn State University, Hershey, [d]the University of Pittsburgh School of Medicine, Pittsburgh; [e]the Cincinnati Children's Hospital and Medical Center; [f]the Pediatrics Section of Allergy, Immunology, and Rheumatology, and [g]the Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison; [h]the Arizona Respiratory Center, University of Arizona, Tuscon; [i]the Washington University School of Medicine, St Louis; [j]the Kaiser Permanente Medical Center, University of California–San Diego, and [k]the University of California-San Francisco; [l]the Boston Children's Hospital, Harvard Medical School; [m]the Children's Memorial Hospital, Chicago; [n]the National Jewish Health, Denver, and [o]the Children's Hospital Colorado, The Breathing Institute, and University of Colorado School of Medicine, Aurora; [p]the University of New Mexico, Albuquerque.

†Dr Strunk is deceased.

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Corresponding author: Jason E. Lang, MD, MPH, Division of Allergy/Immunology and Pulmonary Medicine, Duke Children's Hospital and Health Center, MSRB-1 203 Research Drive Room 127, Durham, NC 27708. E-mail: jason.lang@duke.edu.

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Conclusions: In preschool children off controller therapy, OW is associated with greater asthma impairment and exacerbations. However, unlike older asthmatic patients, OW preschool children do not demonstrate reduced responsiveness to ICS therapy. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Asthma, overweight, obesity, children, infants, exacerbation*

Asthma is one of the most common chronic diseases of childhood and adolescence.[1,2] High body mass index (BMI) status has a poorly defined relationship with asthma severity. According to national asthma guidelines, classification of asthma severity in controller-naive patients depends on impairment of daily functioning by asthma symptoms and risk of exacerbations.[3] Studies involving older youths and adults have found that overweight or obesity status (OW) worsens asthma symptoms,[4-6] asthma-related health care utilization,[6-8] and response to inhaled corticosteroids (ICS).[9-11] For example, Quinto et al[6] studied 32,321 children 5 to 17 years of age within the Kaiser Permanente health system and found that OW was associated with poor asthma control and exacerbations, measured by rescue inhaler and oral steroid dispensing, respectively. However, others have found no association between OW and measures of asthma severity,[12-14] or found that high BMI was associated with reduced (not greater) airway hyperresponsiveness, a central component of asthma.[15-17] It is possible that asthma in childhood may act in the opposite direction by promoting weight gain.[18] Very little data currently exist exploring the effects of OW status on asthma severity in preschool children. In addition, no studies to our knowledge have investigated OW and ICS response in preschoolers. The lack of research of OW status in preschoolers is an important gap in children's health considering that preschool children (<5 years of age) are at a particularly high risk for morbidity stemming from asthma or recurrent wheezing. One-half of all children experience wheezing by age 5 years[19]; roughly one-third of preschool children suffer prolonged episodes of recurrent asthma symptoms[20]; and among preschoolers, asthma symptoms are a leading cause of hospitalizations and emergency department visits. Additionally, the current prevalence of OW in the United States for 2- to 5-year-olds is 27%.[21] Elucidating the factors in preschool children that affect the treatment efficacy of ICS is of particular public health interest. If early life OW status does worsen asthma symptoms and reduces the effectiveness of ICS, early life nutrition and obesity prevention efforts could be intensified and become a critically important intervention.

Currently, ICS are the most effective single antiasthma controller medication available for the prevention of daily symptoms and exacerbations. Therefore, response to daily ICS is an important phenotypic characteristic of childhood asthma. Only a few studies in adults and 1 study in older children[11] have evaluated the effect of OW on ICS treatment response. Studies have demonstrated a reduced response to ICS among adults with high BMI.[9,22,23] In the Childhood Asthma Management Program (CAMP) study, Forno et al[11] found that OW children, compared with normal weight (NW) children, demonstrated a reduced improvement in lung function and asthma-related urgent care use in response to ICS. Using data from 3 large prospective trials of preschool children enrolled in the Childhood Asthma Research and Education (CARE) and AsthmaNet networks, we evaluated the effects of early life OW status on prospectively determined asthma symptom days (AD) and exacerbations in children treated with either ICS (daily or intermittent step up) or placebo. We hypothesized that among both placebo-treated and ICS-treated children, OW status would lead to greater AD and exacerbations.

Abbreviations used
AD: Asthma symptom days
BMI: Body mass index
ED: Emergency department
ICS: Inhaled corticosteroids
INFANT: Individualized Therapy for Asthma in Toddlers
LTRA: Leukotriene receptor antagonist
MIST: Maintenance versus Intermittent Inhaled Steroids in Wheezing Toddlers trial
NW: Normal weight
OW: Overweight/obese
PEAK: Prevention of Early Asthma in Kids trial
SABA: Short-acting β-$_2$-agonists

METHODS

Participant selection

Details of the main studies—Individualized Therapy for Asthma in Toddlers (INFANT [NCT01606306]), Prevention of Early Asthma in Kids (PEAK [NCT00272441]), and Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST [NCT00675584])—have been published.[24-27] All caregivers of participants signed written informed consents. The present *post hoc* study was approved by the Nemours Institutional Review Board (928923-2). We included baseline and intervention period data from 736 preschool-age participants (24-59 months) with mild persistent asthma or recurrent wheezing who were randomized into 1 of 3 multicenter placebo-controlled trials in which they received daily ICS, intermittent ICS, or placebo (see Table E1 in this article's Online Repository at www.jacionline.org for detailed entry criteria). Weights were determined using a calibrated electronic or beam balance scale. Standing height was measured without shoes using a calibrated stadiometer accurate to the nearest millimeter. Age- and sex-adjusted BMI percentiles were calculated using a centralized calculator using Centers for Disease Control and Prevention growth chart data. Because underweight children have also demonstrated more severe asthma,[28] participants with BMI <10th percentile were excluded in this analysis (see Table E2 in this article's Online Repository at www.jacionline.org).

The INFANT study was a multicenter, randomized, double-blind, double-dummy, clinical trial in children 12 to 59 months (n = 300) with persistent asthma, which was factorially linked to the Acetaminophen versus Ibuprofen in Young Children with Asthma (AVICA) study. Because treatment with ibuprofen compared with acetaminophen did not affect asthma outcomes,[29] we included INFANT data in the combined analysis. INFANT participants completed a 2- to 8-week run-in period followed by 3 16-week crossover intervention periods with daily ICS (fluticasone propionate, 88 μg twice daily; GlaxoSmithKline, Brentford, UK), daily leukotriene receptor antagonist (montelukast, 4 mg by mouth; Merck, Whitehouse Station, NJ), and intermittent "as-needed" ICS treatment (fluticasone propionate, 88 μg given whenever 2 inhalations of albuterol sulfate are needed; GlaxoSmithKline). The PEAK study was a multicenter double-blind 2-arm parallel study that randomly assigned 285 participants 2 to 3 years of age with a positive modified asthma predictive index to treatment with either fluticasone propionate (Glaxo SmithKline) 88 μg twice daily or masked placebo for 24 months. The MIST trial was a multicenter, randomized, double-blind, parallel trial that studied 278 children between the ages of 12 and 53 months who had recurrent wheezing and a positive modified asthma predictive index. Participants