Metabolic Dysregulation, Systemic Inflammation, and Pediatric Obesity-related Asthma

Deepa Rastogi¹ and Fernando Holguin²

¹Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York; and ²Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado

Abstract

Obesity-related asthma is a distinct pediatric asthma phenotype. It is associated with higher disease burden, lower pulmonary function, and suboptimal response to current asthma medications. Recent studies have made inroads into elucidating its pathophysiology. Systemic immune responses in obese children with asthma are skewed to a nonatopic T-helper cell type 1 (Th1) pattern that correlates with pulmonary function deficits. The prevalence of metabolic dysregulation is also higher among obese children with asthma than among normal-weight children with asthma. Insulin resistance and dyslipidemia, particularly low levels of high-density lipoprotein (HDL), are associated with lower airway obstruction and low expiratory reserve volume. These associations are independent of truncal and general adiposity and thereby suggest a direct association

between metabolic abnormalities and pulmonary function. Furthermore, insulin resistance is associated with Th1 polarization, whereas low HDL is associated with monocyte activation. Although insulin resistance mediates the association of Th1 polarization with pulmonary function, HDL does not have a similar influence on the association of monocyte activation with pulmonary function. Together, these recent studies have paved the way to the understanding of obesity-related asthma as a distinct asthma phenotype and have begun to identify the complex relationships between metabolic dysregulation, systemic inflammation, and pulmonary function deficits in obese children with asthma. Studies are now needed to elucidate the mechanisms that link metabolic dysregulation and systemic immune responses to pulmonary function.

Keywords: obesity; asthma; children

(Received in original form March 14, 2017; accepted in final form May 8, 2017)

Supported by NHLBI grant K23HL118733 (D.R.).

Author Contributions: Conception of manuscript, D.R.; revision of manuscript for important intellectual content D.R. and F.H.

Correspondence and requests for reprints should be addressed to Deepa Rastogi, M.B. B.S., M.S., Department of Pediatrics, Albert Einstein College of Medicine, 3415 Bainbridge Avenue, Bronx, NY 10467. E-mail: drastogi@montefiore.org

Ann Am Thorac Soc Vol 14, Supplement 5, pp S363–S367, Nov 2017

Copyright © 2017 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.201703-231AW

Internet address: www.atsjournals.org

Rates of both pediatric asthma and pediatric obesity have been increasing in the United States and other developed countries for the past several decades (1, 2). Epidemiological studies done over the past 15 years have suggested that there is an association between pediatric obesity and asthma (3, 4). Longitudinal studies have found obesity to be an independent risk factor for asthma; obese children are at a higher risk of developing asthma than normal-weight children (5). Moreover, children with obesity-related asthma have a more severe disease phenotype characterized by suboptimal response to medications (6) and impaired disease control

(7), with a greater frequency of emergency department visits and hospitalizations (8).

Higher disease in obese children with asthma may be due to their lower pulmonary function (9, 10). They have evidence of augmented lower airway obstruction, with lower FEV₁/FVC ratios (9, 11). Additionally, expiratory reserve volume (ERV) and FRC, which are decreased in obese adults with asthma (12), are also reduced among children with obesity-related asthma, suggesting early onset of effects of obesity on pulmonary function (13–16). However, measures of allergic airway inflammation, including fractional exhaled nitric oxide, tend to be low

or normal in obese children with asthma (17, 18), suggesting that mechanisms other than allergic airway inflammation may underlie obesity-related asthma.

With increased recognition of obesity as a risk factor for asthma and its impact on pulmonary function, recent studies have focused on investigating obesity-mediated mechanisms that may explain the obese asthma pathophysiology. These include the effect of the mechanical load of obesity, particularly truncal adiposity (19), the role of metabolic dysregulation (14, 20), and alterations in the systemic immune milieu (13, 14). Because truncal adiposity is

associated with metabolic dysregulation and obesity-mediated immune responses (21), we speculate that these comorbid conditions, rather than the mechanical effect of adiposity alone, may underlie obesity-related asthma in children. The rationale for this is that not all children with truncal adiposity develop asthma, and there is no evidence supporting a linear relationship between childhood weight gain and asthma. Thus, it is less likely that the fat load alone causes asthma; rather, it is fat load–related complications of metabolic dysregulation and systemic inflammation, which occur in a subset of obese children (22), that likely underlie pediatric obesity-related asthma. However, few studies have investigated these potential mechanisms.

Systemic Inflammation in Obese Asthma Is Similar to but Greater Than Inflammation in Obesity Alone

Obesity is a state of low-grade systemic inflammation initiated by the relative hypoxic environment of rapidly proliferating adipose tissue (23) and supported by leptin, a proinflammatory adipokine (24). The adipose tissue releases cytokines such as monocyte chemoattractant protein 1 that increase monocyte activation and tissue recruitment (25). Circulating monocytes, when activated, form patrolling monocytes that are recruited to adipose tissue to differentiate into adipose tissue macrophages in response to cytokines, including monocyte chemoattractant protein 1 (25–27). These macrophages subsequently mediate both local and systemic inflammatory responses, resulting in the recruitment and activation of T-helper cell type 1 (Th1) cells (24). Activation of Th1 cells further augments the immune response through the production of more proinflammatory cytokines.

In contrast, childhood asthma has classically been associated with a systemic atopic Th2 phenotype, with more Th2 cells in the systemic circulation, resulting in increased differentiation and proliferation of eosinophils, chemotaxis of eosinophils to the airways, and eosinophil-mediated airway damage (28). Key cytokines mediating this progression include IL-4, IL-5, and IL-13, which contribute to the production and survival of eosinophils and their recruitment

into tissues affected by atopic sensitization, including the airway in the case of asthma, the skin in atopic dermatitis, and the nasal mucosa in allergic rhinitis.

Traditionally, Th1- and Th2-mediated immunity result in differential immune cell responses and have been proposed to be mutually inhibitory (29). Although the Th2 phenotype is associated with eosinophilic inflammation (29), Th1 immune responses are associated with neutrophilic inflammation (30). Determining the Th phenotype in obesity-related asthma can thus better characterize the inflammatory pattern mediating the disease process at a molecular and cellular level and thereby facilitate targeted therapeutic interventions.

Given these two distinct patterns of systemic inflammation in obesity and asthma, we and others have investigated the inflammatory phenotype in both preadolescents and adolescents with obesity and asthma. Compared with normal-weight children with asthma and obese control subjects without asthma, obese girls had evidence of noneosinophilic asthma (10). Both preadolescents and adolescents had evidence of systemic Th1 polarization, with an elevated Th1/Th2 ratio, as compared with their normal-weight counterparts (13, 14). Furthermore, Th1 polarization correlated with leptin, an adipokine associated with obesity-mediated inflammation, and IL-6, a cytokine downstream in the leptin inflammatory pathway, suggesting that obesity was driving the Th1 systemic inflammation in obese children with asthma (13). Investigation of monocyte activation patterns in obese adolescents with asthma further validated the role of obesity-mediated inflammation. Obese adolescents with asthma had evidence of monocyte activation, with fewer classical monocytes and more patrolling monocytes in the circulation in obese children with asthma than in healthy control subjects (14). Although the number of classical and patrolling monocytes in obese children with asthma did not differ from that in obese children without asthma, the Th1/Th2 ratio inversely correlated with classical monocytes and directly correlated with patrolling monocytes uniquely in obese children with asthma and not in obese children without asthma, suggesting that obesity-mediated inflammation was more robust in obese children with asthma than in obese control subjects without asthma (14).

Systemic Inflammation Is Associated with Pulmonary Function Deficits among Obese Children with Asthma

Pulmonary function deficits in obese children with asthma have been described extensively. Compared with air trapping observed in the context of lower airway obstruction and increased airway resistance in normal-weight subjects with asthma (31), a lower FEV₁/FVC ratio coexists with lower lung volumes, including lower FRC, ERV, and residual volume (RV) relative to total lung capacity (TLC) (13–16). This constellation of pulmonary function abnormalities suggests that alteration in airway caliber rather than inherent airway hyperresponsiveness may underlie the obese asthma phenotype (12, 32–34). Thus, in pre-post studies on adult bariatric surgery patients, researchers identified improvement in airway responsiveness (35) with improvement in lung volumes (36) and improvement in systemic inflammatory measures (35–37). We have reported an inverse correlation of FEV₁/FVC ratio with biomarkers of Th1 inflammation, including IFN- γ and IFN- γ -induced protein 10, uniquely in obese preadolescent children with asthma (13). Systemic Th1 polarization also inversely correlated with RV, RV/TLC ratio, and FRC in adolescents, suggesting a negative impact of Th1 polarization on lung volumes (14) (Table 1). Although there are limited studies of weight loss in obese children, one study investigating the role of diet-induced weight loss did identify improvement in pulmonary function (38), suggesting that a more physiological weight loss in children is associated with similar benefits in pulmonary mechanics in adults. However, unlike adults, there was no change in systemic inflammation or metabolic measures of insulin resistance and dyslipidemia with weight loss in children (38).

In our population, we also found that both classical and patrolling monocytes were associated with disease burden. Whereas a higher proportion of classical monocytes correlated with better asthma control, a higher proportion of patrolling monocytes correlated with asthma severity (14). Monocyte activation was also associated with pulmonary function (14). C-C chemokine receptor type 2 (CCR2) expression, a marker of monocyte differentiation (39), decreases as

Table 1. Associations of systemic T-helper cell and monocyte patterns with pulmonary function and the mediating effect of metabolic abnormalities

Age Group	Immune Measures	Pulmonary Function Variable	Direction of Correlation	Metabolic Abnormality Mediating Association of Immune Measures with Pulmonary Function
Preadolescents*	Th1/Th2 ratio	FEV ₁ /FVC ratio	Inverse	Not available
Adolescents†	Th1/Th2 ratio	RV	Inverse	Insulin resistance
		RV/TLC ratio	Inverse	Insulin resistance
		FRC	Inverse	Insulin resistance
		IC	Direct	Insulin resistance
	CCR2 expression on classical monocytes	RV	Direct	None
		FRC	Direct	None
	CCR2 expression on patrolling monocytes	RV	Direct	None
		RV/TLC ratio	Direct	None
		FRC	Direct	None

Definition of abbreviations: CCR2 = C-C chemokine receptor type 2; IC = inspiratory capacity; RV = residual volume; Th1 = T-helper cell type 1; Th2 = T-helper cell type 2; TLC = total lung capacity.

*Summarized from Rastogi and colleagues (13).

†Summarized from Rastogi and colleagues (14).

classical monocytes differentiate into patrolling monocytes. We found that CCR2 expression on classical and patrolling monocytes directly correlated with lung volumes, suggesting an inverse association between monocyte activation and lung volumes (14) (Table 1). These relationships were not observed in normal-weight children with asthma. Together, these studies suggest that obesity-mediated systemic nonatopic inflammation is associated with asthma disease burden and pulmonary function deficits, and that these deficits may be reversible with weight loss.

cholesterol levels, and triglycerides), are more prevalent in children with asthma than in children without asthma (20, 41, 42). Moreover, insulin resistance and dyslipidemia are inversely related to pulmonary function (43, 44). Specifically, higher levels of insulin resistance and lower levels of HDL are associated with impaired FEV₁/FVC ratio, and insulin resistance is an independent predictor of ERV when adjusted for general and truncal adiposity (43), suggesting that metabolic abnormalities impact pulmonary function independently of truncal adiposity. Although the underlying

mechanisms by which altered lipids impact pulmonary physiology are not well understood (45), there is evidence that airway smooth muscle cells have insulin receptors and develop a procontractile phenotype when exposed to insulin (46, 47). Although not routinely used in children, statins have been associated with reduced asthma exacerbations (48) and pulmonary function improvement in adults (49), further supporting a role of metabolic dysregulation in pulmonary function deficits.

Moreover, markers of metabolic dysregulation are associated with immune

Metabolic Dysregulation Mediates the Association of Systemic Inflammation and Pulmonary Function among Obese Children with Asthma

In addition to systemic inflammation, metabolic dysregulation is a key complication of obesity. There is evidence to suggest that obesity-mediated inflammation may underlie the development of insulin resistance and dyslipidemia (40). Several recent studies have identified the prevalence of metabolic dysregulation in obese children with asthma. Insulin resistance, its surrogate marker acanthosis nigricans, and dyslipidemia (decreased high-density lipoprotein [HDL], in the context of increased low-density lipoprotein, total

Figure 1. Obesity is associated with systemic inflammatory responses and metabolic abnormalities, which in turn are associated with the obese asthma phenotype in children. The mechanisms by which systemic inflammatory responses and metabolic abnormalities impact pulmonary function in obese children with asthma are not known. Th1 = T-helper cell type 1.

responses observed in obese children with asthma. Insulin resistance was associated with an increased Th1/Th2 ratio (14), and serum HDL levels were negatively associated with patrolling monocyte levels, which are elevated in obesity (14). Because metabolic dysregulation has been associated with inflammatory markers and has also been associated with decreased pulmonary function, its role in mediating the relationship of obesity-mediated immune responses with pulmonary function in obese children with asthma was investigated. It was noted that insulin resistance mediated the association of Th1 polarization with pulmonary function indices, but HDL levels did not influence the association of monocytes with pulmonary function (14) (Table 1). Together, these relationships suggest that there is a complex relationship between metabolic dysregulation, obesity-mediated immune responses, and their association with pulmonary function.

Epigenetic Footprint of Obese Asthmatic Immune Cells Is Distinct from That in Obese Children without Asthma and Normal-Weight Children with Asthma

Whereas atopic inflammatory pathways have been explored extensively in the context of childhood asthma and have led to the development of targeted therapies such as omalizumab (50), those associated with nonatopic immune responses are less well

understood. The Th1 polarization observed in obesity-mediated asthma may be impacted by changes in DNA methylation, reflecting the environmental factors that contribute to the disease phenotype. Pilot investigations of a potential role of epigenetics identified that gene promoter DNA methylation in peripheral blood mononuclear cells from obese individuals with asthma was distinct from that in obese children without asthma, normal-weight children with asthma, and healthy children (51). It revealed DNA hypomethylation of several gene promoters, including the genes chemokine (C-C motif) ligand 5, IL27, IL-2 receptor subunit α , signal transducer and activator of transcription 1, IFN- γ , and T-box transcription factor 21, which are associated with Th1 polarization and monocyte activation, as well as hypermethylation of the gene Fc fragment of IgE receptor II, which is associated with IgE-mediated immune responses, and the genes suppressor of cytokine signaling 2 and 3, and transforming growth factor β 1, which diminish Th cell proinflammatory responses. In addition, several genes associated with immunometabolic responses, including peroxisome proliferator-activated receptor γ , phosphoinositide-3-kinase regulatory subunit 1, and phosphoinositide-3-kinase adaptor protein 1, were hypomethylated, whereas arachidonate 15-lipoxygenase was hypermethylated. Together, this pilot study highlighted that epigenetics may identify differentially activated immunometabolic pathways in obese children with asthma that may serve as potential therapeutic targets for nonatopic pediatric asthma.

Future Directions

Epidemiological and observational studies have shown that clinical features previously described in obese adults with asthma, including high disease burden, lack of medication responsiveness, absence of atopy, and pulmonary function deficits (52, 53), are present in obese children with asthma as early as the preadolescent years. Mechanistic studies have begun to highlight the links between childhood obese asthma and systemic immune and metabolic effects of obesity. The association of disease burden with metabolic abnormalities thus highlights that certain at-risk obese children manifest obesity-mediated complications and their downstream effects on the pulmonary system. The time is ripe to pursue an improved understanding of mechanisms by which systemic metabolic patterns and immune responses impact the local airway (Figure 1). In addition, weight loss studies have reported improvement in disease burden in obese children with asthma. Study of the impact of weight loss interventions using dietary modification, with/without exercise, on metabolic and immune patterns will additionally identify interventions that will be effective in decreasing the burden of obese asthma. Together, these studies will lead to identification of at-risk children and interventions that may prevent or treat obesity-mediated pediatric lung disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- Akinbami LJ, Simon AE, Rossen LM. Changing trends in asthma prevalence among children. *Pediatrics* 2016;137:e20152354.
- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA* 2012;307:483–490.
- Black MH, Smith N, Porter AH, Jacobsen SJ, Koebrick C. Higher prevalence of obesity among children with asthma. *Obesity (Silver Spring)* 2012;20:1041–1047.
- Black MH, Zhou H, Takayanagi M, Jacobsen SJ, Koebrick C. Increased asthma risk and asthma-related health care complications associated with childhood obesity. *Am J Epidemiol* 2013;178:1120–1128.
- Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obes Rev* 2013;14:222–231.
- McGarry ME, Castellanos E, Thakur N, Oh SS, Eng C, Davis A, Meade K, LeNoir MA, Avila PC, Farber HJ, et al. Obesity and bronchodilator response in black and Hispanic children and adolescents with asthma. *Chest* 2015;147:1591–1598.
- Borrell LN, Nguyen EA, Roth LA, Oh SS, Tcheurekdjian H, Sen S, Davis A, Farber HJ, Avila PC, Brigino-Buenaventura E, et al. Childhood obesity and asthma control in the GALA II and SAGE II studies. *Am J Respir Crit Care Med* 2013;187:697–702.
- Belamarich PF, Luder E, Kattan M, Mitchell H, Islam S, Lynn H, Crain EF. Do obese inner-city children with asthma have more symptoms than nonobese children with asthma? *Pediatrics* 2000;106:1436–1441.
- Vo P, Makker K, Matta-Arroyo E, Hall CB, Arens R, Rastogi D. The association of overweight and obesity with spirometric values in minority children referred for asthma evaluation. *J Asthma* 2013;50:56–63.
- Jensen ME, Gibson PG, Collins CE, Wood LG. Airway and systemic inflammation in obese children with asthma. *Eur Respir J* 2013;42:1012–1019.
- Consilvio NP, Di Pillo S, Verini M, de Giorgis T, Cingolani A, Chiavaroli V, Chiarelli F, Mohn A. The reciprocal influences of asthma and obesity on lung function testing, AHR, and airway inflammation in prepubertal children. *Pediatr Pulmonol* 2010;45:1103–1110.
- Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol* (1985) 2010;108:206–211.

- 13 Rastogi D, Canfield SM, Andrade A, Isasi CR, Hall CB, Rubinstein A, Arens R. Obesity-associated asthma in children: a distinct entity. *Chest* 2012;141:895–905.
- 14 Rastogi D, Fraser S, Oh J, Huber AM, Schulman Y, Bhagatani RH, Khan ZS, Tesfa L, Hall CB, Macian F. Inflammation, metabolic dysregulation, and pulmonary function among obese urban adolescents with asthma. *Am J Respir Crit Care Med* 2015;191:149–160.
- 15 Davidson WJ, Mackenzie-Rife KA, Witmans MB, Montgomery MD, Ball GD, Egbogah S, Eves ND. Obesity negatively impacts lung function in children and adolescents. *Pediatr Pulmonol* 2014;49:1003–1010.
- 16 Gibson N, Johnston K, Bear N, Stick S, Logie K, Hall GL. Expiratory flow limitation and breathing strategies in overweight adolescents during submaximal exercise. *Int J Obes* 2014;38:22–26.
- 17 Han YY, Forno E, Celedón JC. Adiposity, fractional exhaled nitric oxide, and asthma in U.S. children. *Am J Respir Crit Care Med* 2014;190:32–39.
- 18 Santamaria F, Montella S, De Stefano S, Sperli F, Barbarano F, Spadaro R, Franzese A. Asthma, atopy, and airway inflammation in obese children. *J Allergy Clin Immunol* 2007;120:965–967.
- 19 Musaad SM, Patterson T, Erickson M, Lindsey M, Dietrich K, Succop P, Khurana Hershey GK. Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant. *J Allergy Clin Immunol* 2009;123:1321–1327.e12.
- 20 Cottrell L, Neal WA, Ice C, Perez MK, Piedimonte G. Metabolic abnormalities in children with asthma. *Am J Respir Crit Care Med* 2011;183:441–448.
- 21 Lee MJ, Wu Y, Fried SK. Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. *Mol Aspects Med* 2013;34:1–11.
- 22 Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004;350:2362–2374.
- 23 Zeyda M, Farmer D, Todoric J, Aszmann O, Speiser M, Györi G, Zlabinger GJ, Stulnig TM. Human adipose tissue macrophages are of an anti-inflammatory phenotype but capable of excessive pro-inflammatory mediator production. *Int J Obes* 2007;31:1420–1428.
- 24 Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005;115:911–919, quiz 920.
- 25 Ferrante AW Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Intern Med* 2007;262:408–414.
- 26 Ferrante AW Jr. The immune cells in adipose tissue. *Diabetes Obes Metab* 2013;15:34–38.
- 27 Dalmas E, Clément K, Guerre-Millo M. Defining macrophage phenotype and function in adipose tissue. *Trends Immunol* 2011;32:307–314.
- 28 Busse WW, Lemanske RF Jr. Asthma. *N Engl J Med* 2001;344:350–362.
- 29 Kay AB. Allergy and allergic diseases. *N Engl J Med* 2001;344:30–37.
- 30 Tateda K, Moore TA, Deng JC, Newstead MW, Zeng X, Matsukawa A, Swanson MS, Yamaguchi K, Standiford TJ. Early recruitment of neutrophils determines subsequent T1/T2 host responses in a murine model of *Legionella pneumophila* pneumonia. *J Immunol* 2001;166:3355–3361.
- 31 Jain N, Covar RA, Gleason MC, Newell JD Jr, Gelfand EW, Spahn JD. Quantitative computed tomography detects peripheral airway disease in asthmatic children. *Pediatr Pulmonol* 2005;40:211–218.
- 32 Watson RA, Pride NB. Postural changes in lung volumes and respiratory resistance in subjects with obesity. *J Appl Physiol* (1985) 2005;98:512–517.
- 33 Salome CM, Munoz PA, Berend N, Thorpe CW, Schachter LM, King GG. Effect of obesity on breathlessness and airway responsiveness to methacholine in non-asthmatic subjects. *Int J Obes* 2008;32:502–509.
- 34 King GG, Brown NJ, Diba C, Thorpe CW, Muñoz P, Marks GB, Toelle B, Ng K, Berend N, Salome CM. The effects of body weight on airway calibre. *Eur Respir J* 2005;25:896–901.
- 35 Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, Raymond D, Poynter ME, Bunn JY, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011;128:508–515.e2.
- 36 Boulet LP, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012;106:651–660.
- 37 Sideleva O, Black K, Dixon AE. Effects of obesity and weight loss on airway physiology and inflammation in asthma. *Pulm Pharmacol Ther* 2013;26:455–458.
- 38 Jensen ME, Gibson PG, Collins CE, Hilton JM, Wood LG. Diet-induced weight loss in obese children with asthma: a randomized controlled trial. *Clin Exp Allergy* 2013;43:775–784.
- 39 Fantuzzi L, Borghi P, Ciolli V, Pavlakis G, Belardelli F, Gessani S. Loss of CCR2 expression and functional response to monocyte chemotactic protein (MCP-1) during the differentiation of human monocytes: role of secreted MCP-1 in the regulation of the chemotactic response. *Blood* 1999;94:875–883.
- 40 Gutierrez DA, Puglisi MJ, Hasty AH. Impact of increased adipose tissue mass on inflammation, insulin resistance, and dyslipidemia. *Curr Diab Rep* 2009;9:26–32.
- 41 Al-Shawwa BA, Al-Huniti NH, DeMattia L, Gershon W. Asthma and insulin resistance in morbidly obese children and adolescents. *J Asthma* 2007;44:469–473.
- 42 Arshi M, Cardinal J, Hill RJ, Davies PS, Wainwright C. Asthma and insulin resistance in children. *Respirology* 2010;15:779–784.
- 43 Rastogi D, Bhalani K, Hall CB, Isasi CR. Association of pulmonary function with adiposity and metabolic abnormalities in urban minority adolescents. *Ann Am Thorac Soc* 2014;11:744–752.
- 44 Forno E, Han YY, Muzumdar RH, Celedón JC. Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. *J Allergy Clin Immunol* 2015;136:304–311.e8.
- 45 Wendell SG, Baffi C, Holguin F. Fatty acids, inflammation, and asthma. *J Allergy Clin Immunol* 2014;133:1255–1264.
- 46 Schaafsma D, Gosens R, Ris JM, Zaagsma J, Meurs H, Nelemans SA. Insulin induces airway smooth muscle contraction. *Br J Pharmacol* 2007;150:136–142.
- 47 Schaafsma D, McNeill KD, Stelmack GL, Gosens R, Baarsma HA, Dekkers BG, Frohwerk E, Penninks JM, Sharma P, Ens KM, et al. Insulin increases the expression of contractile phenotypic markers in airway smooth muscle. *Am J Physiol Cell Physiol* 2007;293:C429–C439.
- 48 Tse SM, Li L, Butler MG, Fung V, Kharbanda EO, Larkin EK, Vollmer WM, Miroshnik I, Rusinak D, Weiss ST, et al. Statin exposure is associated with decreased asthma-related emergency department visits and oral corticosteroid use. *Am J Respir Crit Care Med* 2013;188:1076–1082.
- 49 Alexeeff SE, Litonjua AA, Sparrow D, Vokonas PS, Schwartz J. Statin use reduces decline in lung function: VA Normative Aging Study. *Am J Respir Crit Care Med* 2007;176:742–747.
- 50 Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364:1005–1015.
- 51 Rastogi D, Suzuki M, Greally JM. Differential epigenome-wide DNA methylation patterns in childhood obesity-associated asthma. *Sci Rep* 2013;3:2164.
- 52 Holguin F, Comhair SA, Hazen SL, Powers RW, Khatri SS, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Fitzpatrick AM, et al. An association between L-arginine/asymmetric dimethyl arginine balance, obesity, and the age of asthma onset phenotype. *Am J Respir Crit Care Med* 2013;187:153–159.
- 53 Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, Fitzpatrick AM, Gaston B, Israel E, Jarjour NN, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol* 2011;127:1486–1493.e2.