

OBESITY

Independent and Synergistic Associations of Asthma and Obesity with Systemic Inflammation in Adolescents

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Introduction. Both asthma and obesity often occur in the same individual. Each increases the risk of cardiovascular disease (CVD) with systemic inflammation likely playing a vital role. We examined the independent and synergistic associations of asthma and obesity with systemic inflammation using high-sensitivity C-reactive protein (hs-CRP) levels in adolescents. **Methods.** This study involves the cross-sectional design carried out in the adolescent and respiratory medicine practices in a children's hospital. Out of 124 adolescents (mean age 16.1 ± 2.3 years), who were either of obese ($N = 75$) or of normal weight ($N = 49$). 51 had asthma (18 normal weight and 33 obese). **Results.** hs-CRP levels were higher in obese versus normal weight groups (geometric mean $\pm$ SD: 2.38 ± 2.91 vs. 0.72 ± 3.54 ; $p < .001$), and in the asthmatic versus non-asthmatic groups (geometric mean $\pm$ SD: 1.21 ± 3.71 vs. 1.96 ± 3.28 ; $p = .039$). We found a trend of increasing hs-CRP levels across the four groups ($p < .001$), with the obese asthmatic group having the highest level. In multivariate regression, we found a strong association between obesity and log-CRP ($\beta \pm$ SE: 1.43 ± 0.23 ; $p < .001$) and a moderate association between asthma and log-CRP ($\beta \pm$ SE: 0.48 ± 0.21 ; $p < .028$), with additive synergy between obesity and asthma. **Conclusions.** Both asthma and obesity are independently and synergistically associated with systemic inflammation. These findings underline the need of a multifaceted approach to address CVD risk in adolescence.

Keywords adolescents, asthma, high-sensitivity C reactive protein, obesity

INTRODUCTION

Both asthma and obesity are proinflammatory conditions that are prevalent in adolescents and often occur together in the same individual, especially in those individuals living in urban neighborhoods with higher rates of poverty and air pollution (1–4). Epidemiologic studies in adults confirm that obesity increases the odds of incident asthma in a dose-dependent manner with increasing body mass index (BMI) (5) and, individually, each condition has been shown in adults to increase risk of cardiovascular disease (CVD) (6–8). Although the mechanism for the increased risk of CVD is not fully understood, systemic inflammation is likely to play a role in both the conditions (9).

Obesity is well known to be associated with systemic inflammation in both the adults (10) and adolescents (11). However, studies examining the association between asthma and systemic inflammation have yielded conflicting results in adults (12–14) and limited data are available in adolescents (15, 16). In addition, because of the large number of individuals who have both the conditions, a more complete understanding of the independent and synergistic associations of asthma and obesity with systemic inflammation will help to clarify the role of asthma in CVD risk assessment in obese individuals. Associations, if found, may alter CVD risk assessment

by adding asthma as a CVD risk marker and better control of asthma could potentially decrease CVD risk.

Of the inflammatory markers, high-sensitivity C-reactive protein (hs-CRP) shows a strong association with CVD risk in adults (17), and with subclinical atherosclerosis in adults (18) and children (19). Elevated levels of hs-CRP are now considered as an independent risk factor for CVD in adults (17, 20). However, the potential interactions among asthma, obesity, and hs-CRP level have not been fully characterized in the adolescent age group.

In this study, we aimed to examine the independent and synergistic associations of asthma and obesity with systemic inflammation, using hs-CRP levels, in a clinical population of adolescents living in the Bronx, the borough of New York City with the highest rates of both asthma and obesity (2, 3).

METHODS

Subjects

Subjects were recruited from adolescent and respiratory medicine practices at the Children's Hospital at Montefiore, Bronx, NY, USA, from November 2007 to June 2009. At the time of their scheduled medical appointments, patients were approached by research assistants in the waiting area and given a questionnaire to complete (see, Measures below). Patients aged 12–20 years, had their height and weight measured by the research assistants

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and were recruited for inclusion in the study, if they were either obese (BMI > 95th percentile for age and sex) or normal weight (BMI > 5th and <85th percentile for age and sex) and with or without asthma. Thus, subjects were categorized into four groups according to the presence of asthma and obesity: normal weight non-asthmatic (NWN), normal weight asthmatic (NWA), obese non-asthmatic (ONA), and obese asthmatic (OA).

Patients, who reported having chronic inflammatory conditions such as diabetes, chronic kidney disease, or lupus on the questionnaire and those who reported taking systemic steroids or high-dose inhaled steroids in the 3 months prior to recruitment were excluded to prevent the confounding effects of high-dose steroid use on hs-CRP levels. The study was approved by the Montefiore Medical Center institutional review board (IRB). The written informed consent was obtained from subjects and parents.

Measures

All measures including hs-CRP level, measures of physical fitness, and pulmonary function tests (PFTs) were obtained within 2 weeks of recruitment.

Questionnaire. The questionnaire was developed to include demographic information, medical history, and list of medications used in the 3 months prior to the recruitment. In addition, to assess the asthma severity among asthmatic patients, the questionnaire included three asthma symptom questions asking about frequency of daytime and nocturnal symptoms and frequency of albuterol use, as per the 2007 NHLBI Asthma Expert Panel Report (21).

Anthropometrics and Physical Fitness. Subjects returned to the Clinical Research Center (CRC) for standardized anthropometric measures and measures of physical fitness. A trained research nurse measured the height and weight in light clothing on a Scaletronix® stadiometer and calculated the BMI. BMI percentile was obtained using the Epi Info software produced by the Centers for Disease Control and Prevention (22).

Subjects also completed the Modifiable Activity Questionnaire for Adolescents (23). We used days of vigorous physical activity in the two weeks prior to the visit as a measure of physical activity. To measure physical fitness, subjects completed the 6-min walk test (6-MWT) as per the American Thoracic Society Guidelines (24). The test is easy to administer, better tolerated, and more reflective of activities of everyday life than other walk tests (25). Trained research nurses at the CRC measured the distance that an individual can walk quickly on a flat hard surface in a period of 6 min.

High-sensitivity CRP Level. The research nurse collected blood from the subjects after an 8- to 12-h fast. Samples were centrifuged within 1 h of collection. hs-CRP level was measured using latex-enhanced immunoturbidimetry (CRP ultra wide reagent kit, Equal Diagnostics, Exton, PA, USA) on the Olympus AU400/400 analyzer (Olympus Life and Material Science Europa GmbH, Lismeehan,

Ireland). The analyzer has a lower limit of detection of 0.1 mg/dL.

Pulmonary Function Tests. All subjects returned to the pulmonary function laboratory at the Children's Hospital at Montefiore, where they had PFTs conducted by a respiratory therapist, trained in pulmonary function testing according to the American Thoracic Society guidelines (26), using a VMax 229 spirometer (Sensormedics Corp. Yorba Linda, CA, USA). We used National Health and Nutritional Examination Survey (NHANES) III reference values to obtain the percent predicted values of spirometry indices (27). Indices measured including forced vital capacity (FVC), forced expiratory volume in first second (FEV₁) (a marker of impaired respiratory function), FEV₁/FVC ratio (a marker of lower airway obstruction), and forced expiratory flow (FEF_{25-75%}) (a measure of air-flow in the mid-portion of forced expiration). Normal values for all indices are predicted to be between 80% and 120%.

Asthma Classification. The diagnosis of asthma in adolescents, who identified themselves as having asthma on the questionnaire, was confirmed by using electronic medical records. Patients were designated to have asthma, if PFTs had been performed confirming the diagnosis of asthma or they had a recorded visit either for an exacerbation of asthma or for the management of asthma. Asthma severity was classified using the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report guidelines (21). Study participants with asthma were queried on the frequency of daytime and nocturnal symptoms and the frequency of albuterol use. Pulmonary function testing as mentioned earlier provided the FEV₁ and FEV₁/FVC measures. Based on the responses to the symptom questions and pulmonary function testing, subjects with asthma were classified as having intermittent, mild persistent, moderate persistent, or severe persistent asthma. As recommended by the NHLBI Expert Panel Report guidelines (21), the symptom frequency or PFT value, which classified asthma into the highest severity category, was used for classification.

Statistical Analyses

All variables were evaluated for normal distribution. As hs-CRP was not normally distributed, it was log-transformed for all analyses. Among the four groups, demographic variables, hs-CRP, PFT indices, and 6-MWTD were compared using ANOVA for continuous variables and chi-square test for categorical variables. For continuous data, between group differences were examined by using Bonferroni post hoc analysis and for categorical data, between group differences were examined by using an individual chi-square test. To ensure homogeneity in the two obese groups with and without asthma, we compared the proportion of subjects with severe obesity (BMI ≥ 99th percentile for age and sex) in each group. To ensure homogeneity in the two groups with asthma and with and without obesity, we compared the proportion of subjects with asthma severity in each group. To assess the

CVD risk among all four groups, we compared the proportion of participants in each group with hs-CRP levels ≥ 3 mg/dL, a value that has been shown to be associated with an increased risk of CVD (28).

Bivariate associations of log-CRP with demographic variables, PFT indices, 6-MWTD, physical activity, obesity, and asthma were examined by using *t*-test and Pearson's correlation. To examine the association between log-CRP and asthma severity and vigorous physical activity, ANOVA was used.

To examine the associations between log-CRP, obesity, and asthma, we used multivariate linear regression and adjusted for potential confounders (e.g. age, sex, and race/ethnicity). As higher amounts of physical activity have been associated with lower levels of proinflammatory markers (29), and improved physical fitness is associated with lower prevalence of CVD risk markers (30), we added the reported days of vigorous physical activity in the last 2 weeks (with no days of physical activity as the reference category) as well as the 6-MWTD as the measures of physical activity and physical fitness, respectively, in the model. Obesity was added as a binary variable (yes/no). Asthma was added to the model first as a binary variable (yes/no) and then, in a separate model, according to the severity (no asthma, mild intermittent, mild persistent, moderate persistent, or severe persistent asthma). Finally, the effect modification between obesity and asthma was examined by adding an interaction term (obesity $\times$ asthma) in the existing regression model. Additive synergy

was examined by calculating the sum of change in model R^2 , where either obesity or asthma was added to the primary model and compared with the change in model R^2 , where both were added to the primary model. Model residuals were plotted for the assessment of normality. Analyses were performed using STATA 11.0 (StataCorp LP, College Station, TX, USA). For all analysis, a *p*-value of $<.05$ was considered statistically significant.

RESULTS

Of the 200 eligible subjects who agreed to participate, 128 returned for the study visit and completed all data collection. Thirty-one were normal weight non-asthmatic (NWN), 18 were normal weight asthmatic (NWA), 42 were obese non-asthmatic (ONA), and 33 were obese asthmatic (OA). Subjects who completed the study were not different in age, sex, or race/ethnicity distribution from those who did not (data not shown). Four subjects were excluded from the analyses because their hs-CRP levels were ≥ 15 mg/L, indicating an acute inflammatory process.

In the 124 subjects included in the analyses, mean age was 16.1 ± 2.3 years; 69% were girls; 59% were Hispanic; and 41% black. Table 1 shows the comparison of the demographic variables, hs-CRP levels, PFT indices, and measures of physical activity and physical fitness among the four groups. Normal weight and non-asthmatic subjects were significantly older than the obese subjects.

TABLE 1.—Characteristics of subjects.

	Normal weight		Obese		<i>P</i> -value ^a
	Non-asthmatic (<i>n</i> = 31)	Asthmatic (<i>n</i> = 18)	Non-asthmatic (<i>n</i> = 42)	Asthmatic (<i>n</i> = 33)	
<i>N</i> = 124					
Age, yrs. (mean $\pm$ SD)	17.4 $\pm$ 2.1* [^]	16.3 $\pm$ 2.5	15.7 $\pm$ 2.2*	15.3 $\pm$ 1.9 [^]	<.001
Females, <i>n</i> (%)	26 (84)	11 (61)	29 (69)	19 (58)	.13
Race/ethnicity					
Hispanic, <i>n</i> (%)	21 (68)	13 (72)	25 (60)	14 (42)	.11
Black, <i>n</i> (%)	10 (32)	5 (28)	17 (40)	19 (58)	
BMI, kg/m ² (mean $\pm$ SD)	22.8 $\pm$ 3* [^]	22 $\pm$ 3** ⁺	37.7 $\pm$ 7.5**	38.1 $\pm$ 5.4 ^{^+}	<.001
Severe obesity (BMI > 99th percentile), <i>n</i> (%)	Not applicable	Not applicable	18 (44)	19 (56)	.13
CRP, mg/dL (geometric mean $\pm$ SD)	0.59 $\pm$ 3.7* [^]	0.87 $\pm$ 2.99 ^{†§}	2.19 $\pm$ 3.02* [†]	2.81 $\pm$ 2.9 [§]	<.001
CRP ≥ 3 mg/dL, <i>n</i> (%)	5 (16)*	3 (15) [^]	17 (42)*	21 (62) [^]	<.001
Asthma Severity, <i>n</i> (%)					.5
Intermittent		6 (33)		17 (52)	
Mild persistent	Not applicable	5 (28)	Not applicable	6 (18)	
Moderate persistent		7 (39)		9 (27)	
Severe persistent		0		1 (3)	
FVC, % predicted (mean $\pm$ SD)	98 $\pm$ 13	94 $\pm$ 15	97 $\pm$ 15	99 $\pm$ 17	.78
FEV ₁ , %predicted (mean $\pm$ SD)	96 $\pm$ 10	87 $\pm$ 15	94 $\pm$ 15	92 $\pm$ 16	.16
FEV ₁ /FVC (mean $\pm$ SD)	87 $\pm$ 6	82 $\pm$ 10	86 $\pm$ 5	82 $\pm$ 8	.03
FEF _{25-75%} , predicted (mean $\pm$ SD)	94 $\pm$ 16	77 $\pm$ 23	93 $\pm$ 23	81 $\pm$ 26	.02
6-MWT, feet (mean $\pm$ SD)	1565 $\pm$ 182	1561 $\pm$ 271	1509 $\pm$ 164	1447 $\pm$ 206	.08
Days of physical activity in past 2 weeks:					.005
None	17 (55)	9 (50) [^]	16 (38)*	4 (13)* [^]	
1–5 days	8 (26)	5 (28) [^]	17 (40)*	22 (73)* [^]	
≥ 6 days	6 (19)	4 (22)	9 (21)	4 (13)	

Note: ^aANOVA for continuous variables and chi-squared test for categorical variables.

Similar symbols show significant between group differences in post hoc analyses, using Bonferroni correction for continuous variables and individual chi-squared tests for categorical variables.

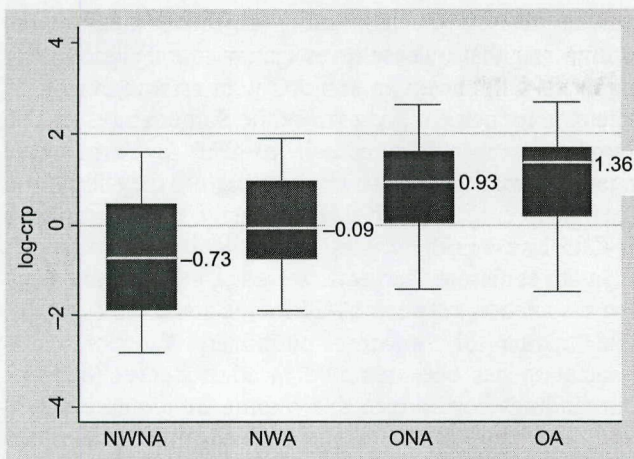


FIGURE 1.—Box plots of log-CRP among the four groups of subjects with and without obesity and asthma.

Note: Trend test across ordered groups: p -value $\leq .001$.

NWNA, normal weight non-asthmatic; NWA, normal weight asthmatic; ONA, obese non-asthmatic; OA, obese asthmatic.

The upper and lower edges of the box represent the 25th and 75th percentiles and the middle line represents the median value of log-CRP. Whiskers represent 1.5 times the inter quartile range.

TABLE 2.—Correlation between CRP and measures of asthma severity.

	CRP	<i>P</i> -value
FVC	−0.06	.74
FEV ₁	−0.22	.02
FEV ₁ /FVC	−0.14	.69
FEF _{25–75%}	−0.13	.71
6-MWTD	−0.06	.51

There was no difference in the sex and racial-ethnic distribution among the groups. Nearly 50% of obese subjects with and without asthma had severe obesity. More than one-third of all subjects had an hs-CRP level ≥ 3 mg/dL, a level that has been associated with increased CVD risk burden in adults (31, 32). And, the proportion of adolescents with hs-CRP levels ≥ 3 mg/dL increased significantly from 16% in the NWNA group to 42% in the ONA group, and to 62% in the OA group. There was no difference in

severity of asthma between the obese and normal weight groups, with only one subject with severe asthma. Of the pulmonary function indices, both FEV₁/FVC ratio and FEF_{25–75%} predicted were significantly lower in the asthmatic groups when compared with the non-asthmatic groups. We found a significant trend in increasing hs-CRP levels among the four groups, with the OA group having the highest median level (Figure 1).

Examining bivariate associations of hs-CRP with obesity and asthma, hs-CRP levels were significantly higher in the obese subjects compared with the normal weight subjects (geometric mean $\pm$ SD: 2.38 ± 2.91 vs. 0.72 ± 3.54 ; $p < .001$) and between the asthmatic and non-asthmatic subjects (geometric mean $\pm$ SD: 1.21 ± 3.71 vs. 1.96 ± 3.28 ; $p = .039$).

Examining the association between hs-CRP levels and pulmonary function indices, we found a significant negative correlation of hs-CRP with FEV₁ (Table 2). No significant correlations were found between hs-CRP and the other pulmonary function indices, or the 6-MWTD. In addition, we found no association between hs-CRP and asthma severity or days of physical activity.

In multivariate regression, after adjusting for age, sex, race, physical activity, 6-MWTD, and obesity, the model explained 30% of the variance in hs-CRP (see, Model 2 in Table 3). A strong association was observed between obesity and log-CRP ($\beta \pm$ SE: 1.43 ± 0.23 ; $p \leq .001$). When asthma was included as a covariate in the model, it explained 33% of the variance in log-CRP (see, Model 3 in Table 3). Asthma was moderately associated with log-CRP ($\beta \pm$ SE: 0.48 ± 0.21 ; $p \leq .05$). Adding a multiplicative term (asthma $\times$ obesity) showed no significant interaction between asthma and obesity in their association with log-CRP. However, we found additive synergy between obesity and asthma. This was done by adding each to the primary model separately and calculating the difference in R^2 and comparing these results with the change in R^2 when both were added to the same model. Our primary regression model (see, Table 3: Model 1) has an R^2 of 0.057. Adding asthma alone to the model resulted in a change in R^2 of 0.022, while adding obesity alone to the model resulted in a change in R^2 of 0.241 (see, Table 3: Model 2). Adding both obesity and asthma to the model resulted in a change in R^2 of 0.272 (see Table 3: Model 3). Thus, changes in model R^2 when both obesity and

TABLE 3.—Regression models of log-CRP with obesity and asthma*.

	Model 1			Model 2			Model 3		
	β	95% CI	<i>P</i> -value	β	95% CI	<i>P</i> -value	β	95% CI	<i>P</i> -value
6 MWTD, feet	0.0003	−0.001, 0.001	.85	0.003	−0.001, 0.001	.599	0.0002	−0.001, 0.001	.676
Activity 1–5 days	0.090	−0.142, 0.932	.15	0.090	−0.393, 0.574	.712	0.016	−0.464, 0.496	.947
Activity > 6 days	−0.374	−0.948, 0.388	.41	−0.372	−0.962, 0.217	.213	−0.378	−0.958, 0.199	.196
Obesity				1.426	0.902, 1.830	<.001	1.432	0.973, 1.892	<.001
Asthma							0.478	0.059, 0.897	.028
Model R^2	0.057			0.298			0.329		
Model <i>p</i> -value	0.23			<.001			<.001		

Note: *All models also adjusted for age, sex, and race/ethnicity.
6-MWTD, 6-min walk test distance.

asthma are in the model (0.272) were greater than the sum of the changes in R^2 with asthma or obesity alone ($0.022 + 0.241 = 0.263$), showing additive synergy between the two conditions.

DISCUSSION

In this sample of adolescents, we found that, after controlling for potential modifying factors, both asthma and obesity are independently associated with systemic inflammation, as measured by hs-CRP. Bivariate associations showed a trend toward higher hs-CRP levels in subjects with both obesity and asthma. This was further noted when examining for an additive interaction in the multivariate regression model, after adjusting for known confounders, suggesting a synergistic association of obesity and asthma with systemic inflammation.

The association between asthma, obesity, and systemic inflammation remains controversial. It has been hypothesized that some cytokines associated with obesity may play a modifying role in asthma. For example, IL-6 has the potential to modulate the T helper 2 (Th2) immunity (33) and TNF- α amplifies airway inflammation (34) and increases airway contractility *in vitro* (35). Studies in the pediatric population report contradictory results in the association between asthma and systemic inflammation. In a longitudinal study, Bekkers et al. recently reported an association between complement factor 3 (C3) and asthma symptoms in children, but no association with CRP (36), whereas Deraz et al. showed a positive association between childhood asthma and CRP in non-obese age and sex-matched children (37). In addition, in a retrospective analysis of over 10,000 children (mean age 9.3 ± 6.3 years) from the NHANES, Michelson et al. found that the association between elevated hs-CRP levels and asthma was most pronounced in subjects with the most severe reported symptoms (16). We found no association between asthma severity and hs-CRP levels. However, our study sample was skewed toward subjects with intermittent or mild persistent asthma. Thus, the interplay between obesity, asthma, and inflammation needs to be evaluated further.

To our knowledge, our finding of a significant independent positive association between asthma and hs-CRP levels using objective measures of asthma diagnosis and severity has not been reported in adolescents. Our use of objective measures of asthma severity including an asthma symptom questionnaire and PFTs and adjustment for physical activity and physical fitness, both known confounders of hs-CRP, adds to the robustness of our findings. Although the duration of physical activity did not show a significant association with hs-CRP in the regression model, studies have shown that compared with obesity, the association between physical activity and hs-CRP may be modest (38).

Our finding of an independent positive association of asthma and hs-CRP levels is in complete concordance with that of Sutherland et al., who studied premenopausal

women in New Zealand using objective measures of asthma diagnosis. These investigators found significantly higher hs-CRP levels in subjects with asthma even after adjusting for percent body fat. While Sutherland et al. also found an expected increase in hs-CRP levels in obese versus normal weight women, unlike us, they found no synergistic association between obesity and asthma with hs-CRP levels (39).

In our adolescent subjects, we found a significant negative association between hs-CRP levels and FEV₁, a reliable marker of impaired pulmonary function. This association has been reported in adult studies (40, 41). Our findings corroborate this finding in adolescent subjects. Mechanistic studies are required to understand the role of inflammation in reducing lung function.

Our finding of a strong positive association between the obesity and elevated hs-CRP levels confirms what is reported in other pediatric (38, 42) and adult studies (43). Analyzing NHANES data, Ford et al. reported the odds of elevated hs-CRP levels in children with a BMI > 95th percentile are four times as high as those with a BMI in the 15th–85th percentile, even after adjusting for age, race, or ethnicity (42). Similarly, in linear regression models, we found that the association between hs-CRP and BMI persisted, even after adjustment for age, sex, and ethnicity.

Over all, more than one-third of our adolescent subjects had serum hs-CRP levels of ≥ 3 mg/dL. The NHANES 1999–2000 data have showed that 15% of adolescents had hs-CRP levels ≥ 3 mg/L (44). These numbers are similar to our normal weight subjects (16% in asthmatic and non-asthmatic groups). However, our obese cohort showed a much higher proportion of subjects with high-risk CRP levels (42% of non-asthmatic and 62% of asthmatic obese subjects). Although these differences can be attributed to other factors that we did not account for, such as low socioeconomic status (45), it is most likely due to the presence of severe obesity in our cohort, where 50% of the subjects were severely obese (BMI > 99th percentile for age and sex). In addition, the prevalence of adolescent obesity has increased from 17.6% (2003–2006) (1) to 18.2% (2009–2010) (46), and it is possible that the proportion of hs-CRP levels ≥ 3 mg/L may be greater even in population studies. We suggest that the high proportion of adolescents with both asthma and obesity, who have very high levels of systemic inflammation, places this already high-risk population at a greater risk of CVD in young and middle adulthood.

Our results need to be viewed in the light of some limitations. First, the cross-sectional nature of the study prevents us from addressing causality. We used hs-CRP as the only marker of systemic inflammation due to its known predictive ability for CVD risk. However, other inflammatory markers may show stronger associations with asthma and asthma severity. An objective measure of physical activity may be more reliable than a validated self-reported questionnaire. Due to the strong inverse association between steroid use and inflammatory markers, we did not include subjects who had used systemic steroids in

the 3 months prior to recruitment, limiting our subjects to those with mild to moderate asthma. It is probable that subjects with severe and/or poorly controlled asthma would show stronger associations with systemic inflammation. In fact, Torren et al. reported a significant risk of CVD-related death in adults with severe asthma (47). Also, we enrolled obese adolescents but not overweight adolescents. This was done to keep a clear distinction between the two groups. Future studies in a larger cohort of adolescents encompassing all weight and asthma severity categories will be helpful to quantify the independent and synergistic effects of obesity and asthma on systemic inflammation more accurately.

Despite these limitations, our study is the first conducted in children and adolescents, that uses objective measures to determine asthma severity, as recommended by the Expert Panel (21), to examine the association between obesity, asthma, and systemic inflammation. Additionally, by adjusting for known confounding factors related to the hs-CRP levels, such as physical activity and fitness, we were able to examine the independent and synergistic associations of asthma and obesity with systemic inflammation.

CONCLUSION

The independent and synergistic associations between systemic inflammation, asthma, and obesity, underline the need for a coordinated approach to public health efforts to decrease the CVD risk burden during childhood and adolescence.

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DECLARATION OF INTEREST

The authors U.I. Khan, C.R. Isasi, D. Rastogi, and S.M. Coupey have no potential, perceived, or real conflicts of interest to disclose.

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REFERENCES

- Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003–2006. *JAMA* 2008; 299:2401–2405.
- NYC Department of Health and Human Hygiene. Community health profiles—Fordham and Bronx Park. 2006. Available at: <http://www.nyc.gov/html/doh/downloads/pdf/data/2006chp-103.pdf>. Accessed August 24, 2011
- Diabetes and Obesity in New York City. In: NYC Department of Health and Mental Hygiene Community Health Survey. 2007.
- Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. *Arch Pediatr Adolesc Med* 1998; 152:1197–1200.
- Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007; 175:661–666.
- Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, Folsom AR. Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study. *Thorax* 2005; 60:633–638.
- Must A, Strauss RS. Risks and consequences of childhood and adolescent obesity. *Int J Obes Relat Metab Disord* 1999; 23(Suppl 2):S2–S11.
- Orio F Jr., Palomba S, Cascella T, et al. Cardiovascular complications of obesity in adolescents. *J Endocrinol Invest* 2007; 30:70–80.
- Luc G, Bard JM, Juhan-Vague I, Ferrieres J, Evans A, Amouyel P, Arveiler D, Fruchart JC, Ducimetiere P; PRIME Study Group. C-reactive protein, interleukin-6, and fibrinogen as predictors of coronary heart disease: the PRIME Study. *Arterioscler Thromb Vasc Biol* 2003; 23:1255–1261.
- Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999; 282:2131–2135.
- Glowinska B, Urban M, Koput A, Galar M. New atherosclerosis risk factors in obese, hypertensive and diabetic children and adolescents. *Atherosclerosis* 2003; 167:275–286.
- Hahtela T, Laitinen LA. Asthma programme in Finland 1994–2004. Report of a working group. *Clinical and experimental allergy: J British Soc Allergy Clin Immunol* 1996; 26(Suppl 1): i-ii, 1–24.
- Jousilahti P, Salomaa V, Hakala K, Rasi V, Vahtera E, Palosuo T. The association of sensitive systemic inflammation markers with bronchial asthma. *Ann Allergy Asthma Immunol* 2002; 89:381–385.
- Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jögi R, Janson C. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. *Thorax* 2005; 60:451–454.
- Huang F, del-Río-Navarro BE, Monge JJ, Torres Alcántara S, Ontiveros JA, Olivos EN, Martínez de Castro NG, Zhao L, Hong E. Endothelial activation and systemic inflammation in obese asthmatic children. *Allergy Asthma Proc* 2008; 29:453–460.
- Michelson PH, Williams LW, Benjamin DK, Barnato AE. Obesity, inflammation, and asthma severity in childhood: data from the National Health and Nutrition Examination Survey 2001–2004. *Ann Allergy Asthma Immunol* 2009; 103:381–385.
- Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, Rimm EB. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004; 351:2599–2610.
- Wang TJ, Larson MG, Levy D, Benjamin EJ, Kupka MJ, Manning WJ, Clouse ME, D'Agostino RB, Wilson PW, O'Donnell CJ. C-reactive protein is associated with subclinical epicardial coronary calcification in men and women: the Framingham Heart Study. *Circulation* 2002; 106:1189–1191.
- Reinehr T, Kiess W, de Sousa G, Stoffel-Wagner B, Wunsch R. Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism, and blood pressure. *Metabolism* 2006; 55:113–118.
- Ikonomidis I, Stamatelopoulos K, Lekakis J, Vamvakou GD, Kremastinos DT. Inflammatory and non-invasive vascular markers: the multimarker approach for risk stratification in coronary artery disease. *Atherosclerosis* 2008; 199:3–11.

21. Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma. In: National Heart Lung and Blood Institute National Asthma Education and Prevention Program. 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>. Accessed August 24, 2011.
22. Division of Public Health Surveillance and Informatics CfDC. Epi Info 2002—Revision 2 In. Division of Public Health Surveillance and Informatics. Center for Disease Control. January 30, 2003
23. Aaron DJ, Kriska AM, Dearwater SR, Anderson RL, Olsen TL, Cauley JA, Laporte RE. The epidemiology of leisure physical activity in an adolescent population. *Med Sci Sports Exerc* 1993; 25:847–853.
24. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166:111–117.
25. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001; 119:256–270.
26. Loeb JS, Blower WC, Feldstein JF, Koch BA, Munlin AL, Hardie WD. Acceptability and repeatability of spirometry in children using updated ATS/ERS criteria. *Pediatr pulmonol* 2008; 43:1020–1024.
27. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U. S. population. *Am J Respir Crit Care Med* 1999; 159:179–187.
28. Rifai N, Ridker PM. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. *Clin Chem* 2001; 47:403–411.
29. Balagopal P, George D, Patton N, Yarandi H, Roberts WL, Bayne E, Gidding S. Lifestyle-only intervention attenuates the inflammatory state associated with obesity: a randomized controlled study in adolescents. [see comment]. *J Pediatr* 2005; 146:342–348.
30. Zeno SA, Kim-Dorner SJ, Deuster PA, Davis JL, Remaley AT, Poth M. Cardiovascular fitness and risk factors of healthy African Americans and Caucasians. *J Natl Med Assoc* 2010; 102:28–35.
31. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* 2007; 56:1010–1013.
32. Maury E, Ehala-Aleksejev K, Guiot Y, Detry R, Vandenhooft A, Brichard SM. Adipokines oversecreted by omental adipose tissue in human obesity. *Am J Physiol Endocrinol Metab* 2007; 293:E656–665.
33. Heijink IH, Vellenga E, Borger P, Postma DS, de Monchy JG, Kauffman HF. Interleukin-6 promotes the production of interleukin-4 and interleukin-5 by interleukin-2-dependent and—independent mechanisms in freshly isolated human T cells. *Immunology* 2002; 107:316–324.
34. Thomas PS. Tumour necrosis factor- α : the role of this multifunctional cytokine in asthma. *Immunol Cell Biol* 2001; 79:132–140.
35. Sukkar MB, Hughes JM, Armour CL, Johnson PR. Tumour necrosis factor- α potentiates contraction of human bronchus in vitro. *Respirology* 2001; 6:199–203.
36. Bekkers MB, Brunekreef B, de Jongste JC, Kerkhof M, Smit HA, Postma DS, Gehring U, Wijga AH. Childhood overweight and asthma symptoms, the role of pro-inflammatory proteins. *Clin Exp Allergy* 2012; 42:95–103.
37. Deraz TE, Kamel TB, El-Kerdany TA, El-Ghazoly HMA. High-sensitivity C reactive protein as a biomarker for grading of childhood asthma in relation to clinical classification, induced sputum cellularity, and spirometry. *Pediatr pulmonol* 2012; 47:220–225.
38. Cook DG, Mendall MA, Whincup PH, Carey IM, Ballam L, Morris JE, Miller GJ, Strachan DP. C-reactive protein concentration in children: Relationship to adiposity and other cardiovascular risk factors. *Atherosclerosis* 2000; 149:139–150.
39. Sutherland TJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008; 178:469–475.
40. Kony S, Zureik M, Driss F, Neukirch C, Leynaert B, Neukirch F. Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP): a population based study. *Thorax* 2004; 59:892–896.
41. Mendall MA, Strachan DP, Butland BK, Ballam L, Morris J, Sweetnam PM, Elwood PC. C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. *Eur Heart J* 2000; 21:1584–1590.
42. Ford ES, Galuska DA, Gillespie C, Will JC, Giles WH, Dietz WH. C-reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Pediatr* 2001; 138:486–492.
43. Rogowski O, Shapira I, Tokar S, Melamed S, Shirom A, Berliner S, Zeltser D. Obesity-related correlation between C-reactive protein and the calculated 10-y Framingham Coronary Heart Disease Risk Score. *Int J Obes (Lond)* 2005; 29:772–777.
44. Ford ES, Giles WH, Myers GL, Rifai N, Ridker PM, Mannino DM. C-reactive protein concentration distribution among US children and young adults: findings from the National Health and Nutrition Examination Survey, 1999–2000. *Clin Chem* 2003; 49:1353–1357.
45. Alley DE, Seeman TE, Ki Kim J, Karlamangla A, Hu P, Crimmins EM. Socioeconomic status and C-reactive protein levels in the US population: NHANES IV. *Brain, Behavior, & Immunity* 2006; 20:498–504.
46. 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.
47. Toren K, Lindholm NB. Do patients with severe asthma run an increased risk from ischaemic heart disease? *Int J Epidemiol* 1996; 25:617–620.

Notice of Correction

The version of this article published online ahead of print on 11 Oct 2012 contained a number of minor typographical errors. These have been corrected for this version.

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