Systemic inflammation mediates the detrimental effects of obesity on asthma control

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ABSTRACT

Background: *Obesity negatively impacts asthma control, but the inflammatory mechanisms are poorly understood.*

Objective: *To explore which systemic inflammatory mediators mediate the effects of obesity on asthma control.*

Methods: *The subjects with stable asthma (n = 108) underwent assessment of clinical characteristics, which included using The Asthma Control Questionnaire (ACQ)-6. Obesity was defined as a body mass index (BMI) of ≥30 kg/m^2, overweight was defined as BMI between 25 to 29.9 kg/m^2, and lean weight was defined as BMI < 25 kg/m^2. Body composition, including fat mass (FM), visceral fat area (VFA), and percentage body fat (PBF) was analyzed by bioimpedance. Serum interleukin (IL) 4, IL-5, IL-8, IL-13, IL-17, chemokine (C-C motif) ligand (CCL) 17, CCL22, leptin, adiponectin, C-reactive protein (CRP), and interferon (IFN) gamma were measured by using ELISA. Linear regression models were fitted according to the Baron and Kenny procedures for mediation analysis.*

Results: *FM (12.73 ± 3.95 versus 18.59 ± 2.95 versus 27.82 ± 5.17 kg; $p < 0.0001$), VFA (65.99 ± 23.17 versus 93.96 ± 10.28 versus 123.10 ± 18.34 cm^2; $p < 0.0001$), PBF (23.86 ± 7.46 versus 30.74 ± 5.08 versus 36.21 ± 6.28 %; $p = 0.0003$) and ACQ-6 values (0.83 [0, 1.17]) versus 1.15 [0.50, 1.75] versus 1.33 [0.83, 1.83] score; $p = 0.002$) were different among lean (n = 52), overweight (n = 37), and obese (n = 19) subjects. Serum levels of leptin, IL-5, IL-13, IL-17, CCL17, CRP, and IFN-gamma in the obese group were significantly elevated compared with the subjects who were lean or overweight (all $p < 0.05$). The mediation analyses found that the effect of obesity, assessed by BMI, on ACQ-6 was significantly mediated through IL-13 and CCL17. Furthermore, IL-13 and CCL17 mediated the effects of body composition (FM, VFA and PBF) on ACQ-6. The effects of obesity assessed by body composition, but not by using BMI, on ACQ-6 were mediated by leptin.*

Conclusion: *Our mediation analysis confirmed that systemic inflammation biomarkers, such as leptin, CCL17, IL-4, and IL-13, mediated the effects of obesity on asthma control. This warrants prospective exploration in this distinct asthma phenotype in the future.*

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Asthma and obesity have increased concurrently over recent decades and coexist in many patients; both conditions have serious health consequences and significant financial costs.[1,2] Obesity increases the risk of asthma incidence by 92%,[2] and, in addition, subjects with asthma and with obesity more likely experience a two- to four-fold risk of worse clinical outcomes, including asthma quality of life, asthma control, and asthma-related hospitalizations,[3–6] which result in more medical costs, by 60%, in the United States.[7] Results of previous studies indicated that "obese asthma" is a distinct clinical phenotype,[8,9] but the mechanisms that link obesity with asthma remain poorly understood.

Obesity leads to a state of low-grade systemic inflammation, which involves adipokines produced by adipose tissue and other proinflammatory mediators produced by other adipose tissue–resident inflammatory cells. Many studies focused on the potential contribution of adipokines in modulating asthma control in

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patients with obesity.[10] Two of the best characterized adipokines are leptin and adiponectin. Leptin, is an important proinflammatory mediator through exaggeration of T-lymphocyte helper (Th) 1 related responses, is increased in subjects with obesity and can increase airway reactivity, and, therefore, may lead to poor asthma control.[10] Adiponectin, traditionally regarded as an anti-inflammatory mediator, is reduced with increasing adiposity and functions to inhibit airway inflammation and airway reactivity.[11] These results indicated that perturbations in adipokines associated with obesity could impact the level of asthma control. In addition, macrophages that infiltrate adipose tissue are considered to be crucial sources of inflammatory mediators in patients with obese asthma.[12] The release of mediators from adipose tissue macrophages into the circulatory system leads to systemic inflammation, which might cause poor asthma control.[13,14]

Also, different subtypes of activated T-lymphocytes promote diverse types of inflammation in asthma, with Th1 cells that produce cytokines (*e.g.*, interferon [IFN] γ) related to cellular immunity, whereas Th2 cells produce cytokines (IL-4, IL-5, and IL-13) related to allergic inflammation. In animal models, obesity has been shown to be associated with an augmented Th1 response and with elevated levels of IFN-γ[15]and an elevated Th17 response with increased IL-17 levels, which contribute to the airway hyperreactivity that has been associated with obesity.[16] Studies also found that overexpression of the IL-13 gene is effective in blocking the progression of obesity, and exercise training for therapy of obesity reduces the expression of the Th2 cytokines IL-4, IL-5, and IL-13.[17,18] C-reactive protein (CRP) is also reported among patients with obese asthma, and high serum CRP is indicated as a potential sensitive marker of asthma control.[8] However, mediation effects of these inflammatory cells and their mediators on asthma control have not been well studied in the context of obesity-related asthma.

To the best of our knowledge, there are few studies that examined systemic inflammatory mediators that might mediate the relationship between obesity and asthma control. In our study, we aimed to characterize systemic inflammatory mediators that relate to adipose tissue, monocyte and T-lymphocyte responses, and to describe their relationship with obesity and asthma control. In addition, we explored whether systemic inflammatory mediators mediate the associations of obesity with asthma control.

METHODS

More details about the methods used are described in the Online Supplemental Data.

Study Design and Participants

This study was undertaken among the Chinese population enrolled in the Severe Asthma Web-based Database, which was coordinated by the Australasian Severe Asthma Network.[19] We conducted a cross-sectional study by recruiting participants (ages ≥18 years) with stable asthma at the Asthma Clinic of West China Hospital (Chengdu, China) from March 2014 to August 2015. Asthma was diagnosed according to the Global Initiative for Asthma[9] and the National Asthma Education and Prevention Program[20] The study was approved by the clinical research and ethics committee of West China Hospital (2014–30), and written informed consent was obtained from all the patients. The clinical trial registration number is ChiCTR-OOC-16009529.[21]

Obesity Assessments

Body mass index (BMI) was calculated, and the body composition was measured.[22] Obesity was defined as a BMI ≥ 30.0 kg/m^2, overweight was 25.0 ≤ BMI < 30.0 kg/m^2, and lean as BMI <25.0 kg/m^2.[23] Body composition, including fat mass (FM), visceral fat area (VFA), and percentage body fat (PBF), was measured by bioimpedance analyzer (Inbody S10, Body Composition Analyzer; Biospace Co., Ltd., Seoul, Korea) operated by the clinical nutritionist (G.P. Chen) according to the InBody S10 user's manual.[24]

Spirometry, Sputum Induction, Fractional Exhaled Nitric Oxide, and Asthma Control Measurements

Before spirometry, fractional exhaled nitric oxide was detected according to guidelines from the American Thoracic Society.[25] Spirometry was conducted by following the American Thoracic Society /European Respiratory Society guidelines.[26] Sputum induction and analysis were performed as described in our previous study.[27] The Asthma Control Questionnaire (ACQ)-6 and the Asthma Quality of Life Questionnaire were applied to assess asthma control and the asthma quality of life, both of which have been well validated.[28–33]

Blood Analysis

Serum inflammatory cytokines, including IL-4, IL-5, IL-8, IL-13, IL-17, CCL17, CCL22, leptin, adiponectin, IFN-γ, and CRP, were detected by using ELISA (RayBiotech, Inc., Norcross, GA).

Statistical Analysis

All statistical analyses for sample size calculation, clinical data, mediation analysis by using the progress outlined by Baron and Kenny[34] and the Sobel test[35] are described in detail in the Online Supplemental Data.

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Table 1 **Subject characteristics grouped by BMI category**

Characteristics	Lean (n = 52)	Overweight (n = 37)	Obese (n = 19)	p Value
Men, no. (%)	21 (40.4)	16 (43.2)	10 (52.6)	0.080
Age, mean ± SD, y*	46.7 ± 16.8	47.5 ± 16.7	44.2 ± 10.8	0.101
Atopy, no. (%), yes	16 (30.8)	7 (18.9)	4 (21.1)	0.404
BMI, mean ± SD, kg/m^2*	22.6 ± 1.59	26.6 ± 1.5#	32.5 ± 2.3#§	<0.0001¶
Body composition, mean ± SD*				
FM value, kg	12.73 ± 3.95	18.59 ± 2.95#	27.82 ± 5.17#§	<0.0001¶
PBF, %	23.86 ± 7.46	30.74 ± 5.08#	36.21 ± 6.28#	0.0003¶
VFA value, cm^2	65.99 ± 23.17	93.96 ± 10.28#	123.10 ± 18.34#§	<0.0001¶
Asthma duration, median (Q1, Q3), y‖	5.6 (3.2, 22.8)	10.0 (3.2, 16.7)	12.7 (5.8, 36.5)	0.221
ACQ-6 score, median (Q1, Q3)‖	0.83 (0, 1.17)	1.15 (0.5, 1.75)#	1.33 (0.83, 1.83)#	0.002¶
AQLQ score, median (Q1, Q3)‖	6.13 (5.52, 6.50)	6.13 (5.52, 6.50)	5.88 (5.16, 6.28)	0.093
Maintenance ICS, no. (%)	3 (5.8)	1 (2.7)	2 (10.5)	0.389
Maintenance ICS, median (Q1, Q3), μg, beclomethasone equivalents/day‖	160 (160, 400)	160 (160, 160)	160 (160, 400)	0.639
FeNO, median (Q1, Q3), ppb‖	34.0 (22.0, 71.5)	22.0 (11.0, 56.0)	27.0 (19.5, 41.5)	0.417
Spirometry, mean ± SD*				
Pre-FEV$_1$, L	2.12 ± 0.79	2.08 ± 0.75	2.29 ± 0.61	0.453
Pre-FEV$_1$, % predicted	72.60 ± 18.45	74.68 ± 24.74	72.94 ± 13.56	0.892
Pre-FEV$_1$:FVC, %	0.67 ± 0.13	0.66 ± 0.16	0.66 ± 0.10	0.077

BMI = Body mass index; SD = standard deviation; FM = fat mass; PBF = percentage body fat; VFA = visceral fat area; Q = quartile; ACQ-6, The Asthma Control Questionnaire (ACQ)-6; AQLQ = Asthma Quality of Life Questionnaire; ICS = inhaled corticosteroid; FeNO = fractional exhaled nitric oxide; FEV$_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; ANOVA = analysis of variance.
**Data are normally distributed.*
#ANOVA test with Bonferroni posttest: vs. patients with lean asthma, $p < 0.025$.
§ANOVA test with Bonferroni posttest: vs. patients with overweight asthma, $p < 0.025$.
¶Statistical significance.
‖Data are non-normally distributed.

RESULTS

Clinical and Inflammatory Characteristics

One hundred and eight subjects were included. The mean ± standard deviation for BMI was 25.7 ± 4.0 kg/m^2, and the median (quartile 1, quartile 3) ACQ-6 score was 0.92 (0.47, 1.50) (Online Supplemental Table 1). We also compared these characteristics grouped by BMI categories (Table 1). As expected, significant differences in BMI, FM, PBF, and VFA values among the three groups were observed (all $p < 0.001$). The participants who were overweight and obese had higher FM, PBF, and VFA values than the participants who were lean ($p < 0.025$). There also were significant differences in the ACQ-6 score among the three BMI categories ($p = 0.002$). The patients who were overweight and obese and with asthma had higher ACQ-6 scores in comparison with the patients who were lean and with asthma ($p < 0.025$). Comorbid conditions, presented in Online Supplemental Table 2, were evenly distributed across the three groups (all $p < 0.05$). For systemic inflammatory mediators, the subjects who were obese had higher levels of leptin ($p < 0.001$), CCL17 ($p < 0.001$), IL-5 ($p < 0.001$), IL-13 ($p = 0.004$), IL-17 ($p = 0.006$), CRP ($p = 0.003$), and IFN-γ ($p = 0.020$) compared with the lean with asthma group. The overweight group had higher leptin levels ($p = 0.002$) compared with the lean with asthma group (Fig. 1).

Mediation Effects of Systemic Inflammation Mediators

Whether systemic inflammation mediated the effects of obesity on asthma control was explored, and the results were presented, adjusted for age, gender, atopy, medication use, and forced expiratory volume in 1 second percentage predicted. First, we examined the associations among obesity, asthma control, and systemic inflammation mediators. Asthma control was significantly related to BMI ($\beta = 0.037$; $p = 0.019$), FM

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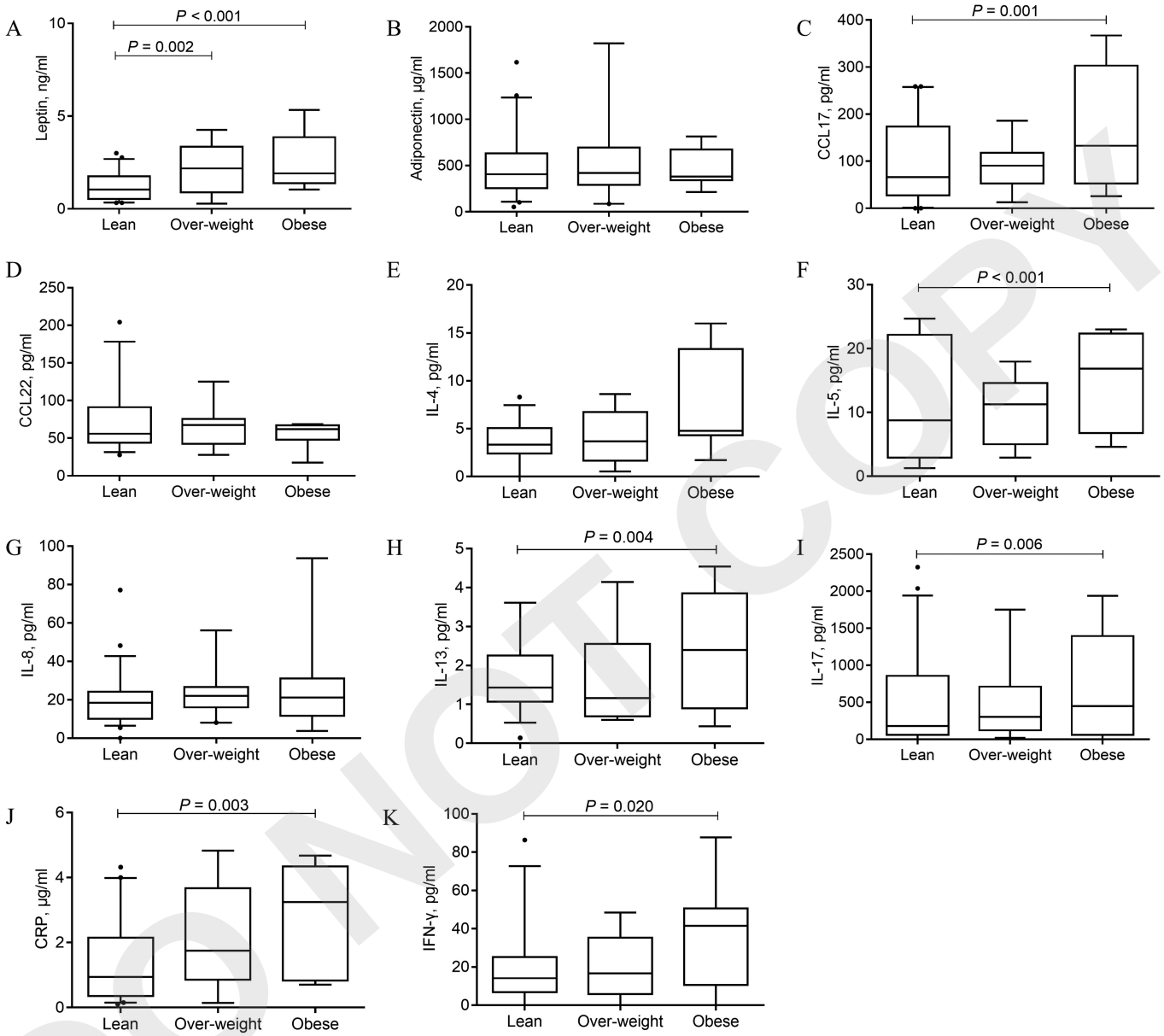

Figure 1. *Systemic inflammatory mediators in subjects with asthma grouped by BMI category. Systemic inflammatory mediators such as (A) leptin, (B) adiponectin, (C) CCL-17, (D) CCL22, (E) IL-4, (F) IL-5, (G) IL-8, (H) IL-13, (I) IL-17, (J) CRP, and (K) IFN-γ in subjects with stable asthma grouped by BMI. BMI = Body mass index; CCL = chemokine (C-C motif) ligand; IL = interleukin; CRP = C-reactive protein; IFN = interferon.*

(β = 0.056; p = 0.021), VAF (β = 0.012; p = 0.035) and PBF values (β = 0.063; p = 0.018) (Online Supplemental Table 3). BMI, FM, VFA, and PBF values were significantly associated with IL-13, CCL17, and leptin ($p < 0.05$). VFA and PBF values were also significantly associated with IL-8 and IL-4 levels ($p < 0.05$) (Online Supplemental Table 4). Furthermore, asthma control was significantly related to IL-13 (β = 0.109; p = 0.038), CCL17 (β = 0.003; p = 0.046), leptin (β = 0.238; p = 0.024), and IL-4 levels (β = 0.103; p = 0.034) (Online Supplemental Table 3).

Second, we explored combined effects to determine which systemic inflammatory mediators mediated the relationship between obesity (measured by using BMI and body composition) and asthma control (Online Supplemental Table 5). Sobel tests (Table 2) were further used to confirm these mediations. IL-13 (β = 0.129; p = 0.038) and CCL17 levels (β = 0.004; p = 0.058) but not BMI remained significantly associated with ACQ-6 score (Online Supplemental Table 5). The Sobel test also confirmed the significant mediatory effect of IL-13 (z = 2.134; p = 0.033) (Table 2).

Analysis of inflammatory cytokines as potential mediators of the relationship between FM and ACQ-6 score produced similar results. IL-13 (β = 0.196; p = 0.010; Sobel test: z = 1.981, p = 0.048), CCL17 (β =

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Table 2 **Mediation effects validated by Sobel tests***

Inflammatory Mediators	BMI			FM			VFA			PBF		
	z	±SE	*p*	*z*	±SE	*p*	*z*	±SE	*p*	*z*	±SE	*p*
Leptin	1.079	0.014	0.281	1.885	0.022	0.059#	2.350	0.008	0.019#	2.007	0.042	0.045#
Adiponectin	0.346	0.012	0.729	0.116	0.013	0.908	0.360	0.003	0.719	0.172	0.012	0.864
CCL17	1.885	0.003	0.059#	2.003	0.020	0.045#	2.163	0.244	0.031#	2.489	0.004	0.013#
CCL22	0.200	0.002	0.842	0.176	0.003	0.860	0.130	0.001	0.897	0.158	0.002	0.874
IL-4	0.977	0.004	0.329	0.490	0.002	0.624	2.145	0.004	0.032#	2.138	0.016	0.033#
IL-5	0.267	0.003	0.789	0.677	0.010	0.498	0.666	0.002	0.505	0.689	0.010	0.491
IL-8	0.468	0.004	0.640	0.481	0.007	0.630	0.329	0.003	0.742	0.329	0.012	0.742
IL-13	2.134	0.031	0.033#	1.981	0.047	0.048#	2.277	0.006	0.023#	3.722	0.004	0.001#
IL-17	0.825	0.025	0.409	0.703	0.028	0.482	0.584	0.006	0.559	0.744	0.028	0.457
CRP	0.550	0.005	0.582	0.041	0.005	0.967	0.019	0.001	0.001#	0.088	0.007	0.930
IFN-γ	0.222	0.007	0.824	0.824	0.010	0.410	0.794	0.002	0.427	0.803	0.009	0.422

BMI = Body mass index; FM = fat mass; VFA = visceral fat area; PBF = percentage body fat; SE = standard error; CCL = chemokine (C-C motif) ligand; IL = interleukin; CRP = C-reactive protein; IFN-γ = interferon gamma; FEV_1 = forced expiratory volume in 1 second.
**All models were adjusted for age, gender, medication use, and FEV_1% predicted.*
#Statistical significance.

0.005; $p = 0.017$; Sobel test: $z = 2.003$; $p = 0.045$), and leptin ($\beta = 0.248$; $p = 0.027$; Sobel test: $z = 1.885$, $p = 0.059$) were found to mediate the relationship between the FM value and the ACQ-6 score (Table 2 and Online Supplemental Table 5). In addition, IL-13 ($\beta = 0.239$; $p = 0.048$), CCL17 ($\beta = 0.383$; $p = 0.032$), leptin ($\beta = 0.534$; $p = 0.001$), and IL-4 levels ($\beta = 0.141$; $p < 0.001$) were inflammatory mediators of the association between the VFA value and asthma control (Online Supplemental Table 5). The Sobel tests confirmed the significant mediation effects of IL-13 ($z = 2.277$; $p = 0.023$), CCL17 ($z = 2.163$; $p = 0.031$), leptin ($z = 2.350$; $p = 0.019$), and IL-4 levels ($z = 2.145$; $p = 0.032$) (Table 2). Furthermore, IL-13 ($\beta = 0.196$; $p = 0.004$), CCL17 ($\beta = 0.005$; $p = 0.033$), leptin ($\beta = 0.466$; $p = 0.044$), and IL-4 levels ($\beta = 0.147$; $p = 0.002$) were the inflammatory mediators that mediated the relationship between PBF and ACQ-6, and these were confirmed ($z = 3.722$, $p = 0.001$; $z = 2.489$, $p = 0.013$; $z = 2.007$, $p = 0.045$; and $z = 2.138$, $p = 0.033$) by Sobel testing (Table 2).

DISCUSSION

To the best of our knowledge, few studies were designed to investigate the involvement of several diverse, sensitive biomarkers of systemic inflammation in the relationship between obesity and asthma control by using mediation analysis. We reported that the subjects who were obese had worse asthma control and elevated levels of systemic inflammatory mediators, including leptin, IL-5, IL-13, IL-17, CCL17, CRP, and IFN-γ, compared with patients who were lean or patients who were overweight. The mediation analyses indicated that the effect of obesity on asthma control was mediated through leptin, IL-13, and CCL17, which indicated that obesity negatively influenced asthma control, partly through these systemic mediators, and underscored the importance of assessing systemic inflammatory profiles in patients who were obese to further understand the complexity of this phenotype of asthma.

The potential contribution of adipokines in modulating asthma control has been explored in previous studies, which showed an increased level of leptin in obese asthma and enhanced neutrophilic airway inflammation and Th1-related responses.[36–38] Leptin as an adipocyte-derived hormone, is known to have pleiotropic functions in both innate and adaptive immunity. Experimental mouse studies indicated an augmenting role for the leptin axis in airway hyperresponsiveness, possibly independently of Th2 inflammation but *via* a direct effect of leptin on airway smooth muscle.[38] In addition, leptin was sufficient to induce the production of proinflammatory cytokines from primary macrophages derived from the subjects who were obese and with asthma, which may contribute to the pathogenesis of airway diseases associated with obesity.[39,40] Our study supported the important role of leptin in mediating the association between obesity and poor asthma control.

In addition to adipocytes, macrophages that infiltrate adipose tissue are crucial sources of inflammatory mediators in obese asthma.[12] Therefore, we investigated the mediation effects of three macrophages-derived mediators, which included CCL17, CCL22, and IL-8.[13]

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CCL17 and CCL22 are produced in M2 cells but chemokine (C-X-C motif) ligand 8 (CXCL-8) (IL-8) is expressed in M1 cells. One previous study showed that the CCL17 level in both serum and sputum of patients with asthma was significantly increased compared with healthy control subjects.[41] The expression of CCL17 messenger RNA was also significantly increased in lung macrophages from both sputum and bronchial lavage fluid in patients with asthma.[42] However, there were few studies that explored CCL17 expression in obese asthma until now.

Our study indicated that the serum CCL17 level was significantly elevated in the subjects with obese asthma than in the subjects who were lean and those subjects who were overweight, which positively correlated with body composition and asthma control. Our results were consistent with the study by Mraz *et al.*,[43] which found that the subjects who were obese had increased CCL17 messenger RNA expression in subcutaneous adipose tissue, which indicated that the potential source of CCL17 would potentially be produced from adipose tissue macrophages. It is interesting that an increased CCL17 level as an M2 biomarker in obese asthma did not support the established hypothesis that obesity shifted the immune phenotype from M2 macrophage polarization to M1.[44] Our study indicated that CCL17 played a potential role in the pathogenesis of airway inflammation in obese asthma, but this needs to be further explored.

The gene for CCL22 is located on chromosome 16 in humans, along with CCL17. Expression of the CCR4-specific ligand CCL22 was strongly upregulated on airway epithelial cells on allergen challenge, which indicated an involvement of this receptor–ligand axis in the airway inflammation in asthma. However, the mediation effect of systemic CCL22 on asthma control was not identified. IL-8 (CXCL8), mainly produced by macrophages, is involved in chemotaxis of neutrophils to the site of inflammation. In comparison with healthy subjects, the IL-8 level in the bronchial lavage fluid from patients with asthma was increased, which correlated with the percentage neutrophils in the tracheal aspirates.[45,46] Furthermore, in the subjects who were obese, IL-8 released into the circulation caused by an increased number of macrophages in the M1 proinflammatory state may modify the airway inflammatory phenotype, ventilatory pattern, and perception of symptoms, which may affect asthma control.[47] This indicated that there would be an interactive relationship among systemic IL-8, airway inflammation, and asthma control. However, consistent with findings from the study by Sutherland *et al.*,[48] our study showed no significant difference in systemic IL-8 levels in subjects with obese asthma compared with their lean counterparts, which could be explained by the effects of atopy on the systemic inflammation in obese asthma.[49]

Previous studies indicate that Th2 cytokines are critical mediators of chronic airway inflammation[50] and enhanced bronchial hyperresponsiveness.[51] Due to the crucial role for this pathway in the pathogenesis of asthma, there is an interest in the role of Th2 cytokines, including IL-4, IL-13, and IL-5, in the obese asthma phenotype. In this study, the subjects who were obese had a trend toward increased serum IL-4 levels, similar to that obtained from a controlled observational study,[48] in which there were significantly elevated levels of IL-4 in subjects who were obese compared with subjects who were lean and with asthma. Furthermore, IL-4 was a mediator of the obesity on asthma control in our subjects. It was shown that increased systemic IL-4 levels resulted in an enhanced response to allergic or other triggers in subjects who were obese and with asthma, which leads to increased asthma symptoms and poor asthma control.[52]

Interestingly, in our study, IL-13 levels were markedly elevated in the obese asthma group and the mediation effects were also significant, which, to our knowledge, has not been observed in human studies before. Analysis of recently published data indicated that IL-13 levels may be increased in patients who were obese due to increased production by adipocytes or innate lymphoid cells but not Th2 cells.[53] In addition, Darkhal *et al.*[17] previously identified that the overexpression of the IL-13 gene in high-fat diet fed mice inhibits adipose tissue inflammation and blocks high-fat diet induced obesity, which provides evidence for the effects of IL-13 overexpression in preventing obesity. Therefore, in obese asthma, the elevated IL-13 level and the repressed adipose inflammation possibly exerted by elevated IL-13 levels may contribute to the metabolic benefits and block obesity.[53]

Also, although raised IL-13 levels could play a unique protective role by limiting adipose tissue inflammation and obesity, it may, nonetheless, worsen asthma control. In this study, we confirmed that the IL-5 level was elevated in the patients who were obese compared with patients who were lean and with asthma, which was similar to the recently published study that found that obesity was associated with elevated sputum IL-5 levels in asthma.[54] In addition, IL-5 deficiency has been shown to lead to adiposity.[55] These findings indicated that IL-5 might be a potential mediator for the association between obesity and uncontrolled asthma. In addition, consistent with the results from Sutherland *et al.*,[48] blood levels of IFN-γ were significantly higher in the subjects who were obese and with asthma compared with subjects with asthma who were not obese. However, we did not observe a mediation effect of systemic IL-5 or IFN-γ levels on the

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relationship between obesity and asthma control, which may be due to our cross-sectional study design.

One advantage of this study was the alternative measures of obesity that we used. BMI is limited as a marker of adiposity[56] because it does not take into account gender differences in muscle mass, proportion of fat versus lean tissue, or body fat distribution. Our study confirmed that body composition analysis provided a more accurate description of adiposity. However, one potential limitation of our study was the cross-sectional design. The results of mediation analysis essentially represent a correlation between variables, which do not indicate the causality. Also, some comorbid conditions may induce systemic inflammation and further affect asthma control. Our study did not adjust for the effects of the comorbid conditions on the relationship between obesity and asthma control because these effects were evenly distributed among the three groups (Online Supplemental Table 2).

CONCLUSION

We showed that systemic inflammation biomarkers, such as leptin, CCL17, IL-4, and IL-13, mediated the effects of obesity on asthma control. These mediation effects indicated that obesity negatively influenced asthma control, partly through these mediators, and underscored the importance of assessing systemic inflammatory profiles in patients who were obese to better understand this distinct phenotype of asthma. This warrants further prospective exploration in this distinct asthma phenotype.

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