

# Visceral obesity is associated with clinical and inflammatory features of asthma: A prospective cohort study

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## ABSTRACT

**Background:** Although studies have consistently linked obesity and asthma, the potential influence of visceral obesity on asthma has not been well investigated.

**Objective:** To study the associations of visceral fat area (VFA) and clinical and inflammatory features of asthma and to further explore the effects of VFA on the future risk of asthma exacerbation.

**Methods:** A 12-month prospective cohort study based on the Australasian Severe Asthma Network was designed to observe patients with stable asthma grouped by the median value of VFA. The clinical and inflammatory features of asthma were compared between the low VFA (VFA<sup>low</sup>) and high VFA (VFA<sup>high</sup>) groups. Relationships between VFA and clinical and inflammatory features of asthma were analyzed by using correlation analysis. Univariate and multivariable negative binomial regression analyses were performed to investigate the association of VFA with exacerbations within a 12-month follow-up period.

**Results:** The patients in the VFA<sup>high</sup> group were older and had a longer asthma duration. Interleukin (IL) 6 and IL-8 in sputum were higher, whereas fractional exhaled nitric oxide (FeNO) and blood eosinophils were lower in the VFA<sup>high</sup> group. Gender-differentiated correlations of VFA with clinical and inflammatory variables were observed in age, FeNO, immunoglobulin E, blood total white cells and neutrophils, and sputum IL-1 $\beta$  and IL-8. Furthermore, compared with the VFA<sup>low</sup> group, the VFA<sup>high</sup> group was at significantly increased risk of moderate-to-severe exacerbations (adjusted incidence rate ratio [IRR] 1.55 [95% confidence interval {CI}, 1.06–2.28;  $p=0.025$ ), severe exacerbations (adjusted IRR 2.25 [95% CI, 1.26–4.04];  $p=0.007$ ), and emergency visits (adjusted IRR 5.33 [95% CI, 1.78–17.16];  $p=0.003$ ).

**Conclusion:** The level of VFA was associated with specific clinical and inflammatory characteristics of asthma. Furthermore, VFA, as an independent risk factor, was associated with an increased risk of exacerbations. It indicated that VFA would provide more potential clinical implications for asthma management.

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Obesity has increased dramatically and has been reported to be an increased risk factor for asthma.<sup>1</sup> Further epidemiologic studies confirm that obesity is

associated with severity, treatment response, and control of asthma.<sup>2–4</sup> The potential mechanisms included limited lung function,<sup>5</sup> increased airway hyperreactivity,<sup>6</sup> systemic inflammation, and gut microbiome.<sup>7,8</sup> Although it indicated that obesity is consistently linked with asthma,<sup>1,9–12</sup> the association between obesity and asthma outcome is complex.

Meanwhile, obesity can be classified into different types assessed by a corresponding obesity index, and different types of obesity may influence asthma risk differently.<sup>13</sup> Most previously published studies used body mass index (BMI) as the obesity index because of its clinical utility.<sup>2,14–18</sup> However, the disadvantages of BMI are becoming increasingly apparent. For example, Hasegawa *et al.*,<sup>15</sup> Rodrigo *et al.*,<sup>16</sup> and Mosen *et al.*<sup>2</sup> found that general obesity, which is assessed by using BMI, is associated with worse asthma outcomes, especially asthma-related hospitalizations. But Thomson *et al.*<sup>17</sup> and Gonzalez-Barcala *et al.*<sup>18</sup> did not find similar results by using BMI, which indicated that BMI would not perfectly estimate adiposity, distinguish muscle from fat, and reflect body fat distribution.<sup>19,20</sup> Furthermore, Tavasoli *et al.*<sup>21</sup> explored the relationship

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between central obesity (assessed by waist-to-hip ratio [WHR] and waist circumference [WC]) and asthma outcomes, which suggests that central obesity was associated with an increased risk of asthma attacks.

Recently, more and more studies paid attention to visceral obesity, especially the visceral fat area (VFA), which has been an established risk factor for multiple diseases, including diabetes and cardiovascular disorders.<sup>22,23</sup> Although Goudarzi *et al.*<sup>14</sup> found that VFA was significantly associated with asthma symptoms, they did not explore the relationship between VFA and inflammatory features of asthma, and did not find any significant associations of VFA with future exacerbations. Few studies have yet been designed to explore the relationship of visceral obesity with asthma features and exacerbations in a longitudinal study. Therefore, we conducted a prospective 12-month cohort study to investigate the possible correlations between VFA and clinical and inflammatory features of asthma, and to further explore the relationships between VFA and asthma exacerbations in a real-world setting.

## METHODS

### Study Design and Subjects

This was a prospective noninterventional cohort study with a follow-up period of 12 months in a real-world setting based on the ongoing collection data of the Australasian Severe Asthma Network,<sup>24</sup> in which treatments received by patients during this study were determined by standard practices and discretion of their treating physicians. The study was approved by the institutional review board at West China Hospital, Sichuan University (Chengdu, China) (2014–30). Subjects ages  $\geq 18$  years old and with asthma were consecutively recruited from the asthma clinic at West China Hospital, Sichuan University, from March 2015 to August 2018. All the subjects gave written informed consent. The detailed inclusion and exclusion criteria are described in the Online Supplemental Material.

### Data Collection and Clinical Assessments

Baseline clinical data, including sociodemographics, asthma history, medications, history of previous exacerbations, comorbidities, the Asthma Control Questionnaire (ACQ),<sup>25</sup> and the Asthma Quality of Life Questionnaire (AQLQ)<sup>26</sup> were collected. At the same time, all the participants underwent the following assessments: spirometry, fractional exhaled nitric oxide (FeNO), atopy, body composition, sputum induction and analysis, and blood analysis. Before spirometry, FeNO was detected by using the NIOX analyzer (Aerocrine, Solna, Sweden) according to the American Thoracic Society (ATS) guideline.<sup>27</sup> Spirometry was performed according to ATS and European Respiratory Society standards by using spirometry (model 6200; SensorMedics Corp., Yorba Linda, CA).<sup>28</sup> Atopy was

assessed by skin-prick testing with common aeroallergens, as described in our recently published studies.<sup>29,30</sup>

### Anthropometric Measurements

The participants were weighed (the detection limit is 0.1 kg for weight) while they were wearing light clothing and no shoes, and height (the detection limit is 0.5 cm for height) was measured with no shoes. WC and hip circumference were measured, by the same physician (K. Deng, X. Zhang and Y. Liu), at the navel and at the maximum posterior protuberance of the buttocks, respectively, with the patient in a standing position. BMI and WHR were calculated. Body composition, including the visceral fat area (VFA) (in  $\text{cm}^2$ ), fat mass (FM) (in kg), and the percentage body fat (PBF), was measured by using the bioimpedance analyzer (Inbody S10, Body Composition Analyzer; Biospace Co., Ltd., Seoul, Korea) according to the InBody S10 user's manual.<sup>31</sup>

### Sputum Induction and Analysis

Sputum was induced and analyzed as described in our previous study.<sup>32</sup> Total and differential sputum cell counts and sputum inflammatory biomarkers, including interleukin (IL) 1 $\beta$ , IL-4, IL-6, IL-8, IL-17A, and tumor necrosis factor  $\alpha$  were measured. The detailed information is described in the Online Supplemental Material.

### Blood Analysis

Total and differential blood cell counts and serum immunoglobulin E (IgE) levels were measured. The detailed information is described in the Online Supplemental Material.

### Asthma Outcomes

In this study, the enrolled patients were divided to the low VFA (VFA<sup>low</sup>) and high VFA (VFA<sup>high</sup>) groups based on the VFA median levels at baseline. All enrolled patients were followed up for a 12-month period by face-to-face visits or telephone calls. Asthma outcomes included moderate-to-severe exacerbations that presented as unscheduled visits, emergency visits, hospitalizations, or intensive care unit admissions. The detailed definitions are described in the Online Supplemental Material.

### Statistical Analyses

Continuous variables of normal and non-normal distributions were expressed as mean  $\pm$  standard deviation (SD) and median (interquartile range), respectively. Categorical data were presented as frequencies and proportions. Differences between groups were analyzed with the *t*-test or the Kruskal–Wallis test in continuous variables, and the  $\chi^2$  test or the Fisher exact test in categorical variables, as appropriate. Correlations were analyzed by using Pearson or Spearman coefficient tests.

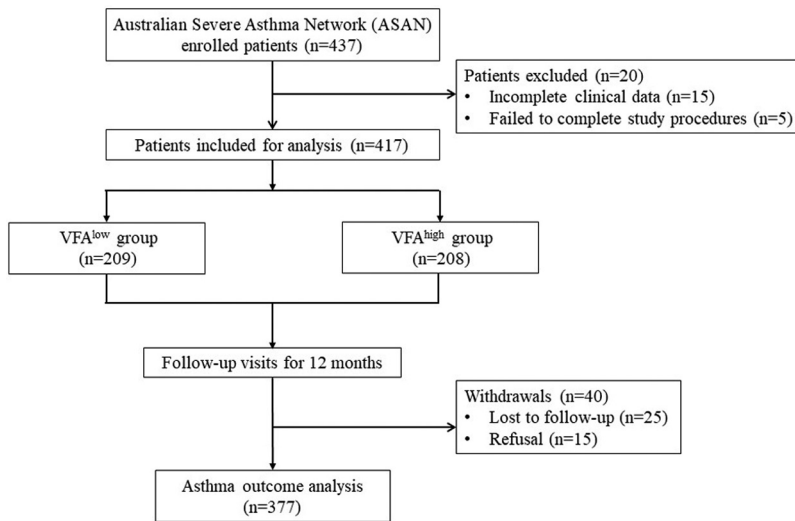


Figure 1. Flow chart of the study.

Furthermore, we calculated the incidence rate ratio (IRR) with 95% confidence interval (CI) by using negative binomial regression models to evaluate the relationships between VFA and asthma exacerbations. In addition, models were adjusted for gender, age, atopy, smoking, asthma duration, inhaled corticosteroid (ICS) dose (beclomethasone dipropionate equivalent) ( $\mu\text{g}/\text{day}$ ) at study baseline and forced expiratory volume in 1 second ( $\text{FEV}_1$ ) percent predicted (%pred.) Adjusted IRR with 95% CI were also calculated. Statistical analysis was performed by using the IBM SPSS 21.0 software (SPSS, Inc, Chicago, IL). A two-sided  $p$  value of  $\leq 0.05$  was considered statistically significant.

## RESULTS

### Characteristics of Patients with Asthma Grouped by VFA

A total of 417 patients were enrolled in this study (Fig. 1). The clinical and inflammatory characteristics were presented in patients grouped by VFA (Tables 1 and 2; Fig. 2). As was indicated by VFA, the patients in the VFA<sup>high</sup> group had significantly elevated BMI, WHR, FM, and PBF values as the body composition than those in the VFA<sup>low</sup> group (all  $p < 0.001$ ). Although the patients in the VFA<sup>high</sup> group were older ( $p = 0.001$ ) and had a longer asthma duration ( $p = 0.040$ ), we found no difference in ACQ, AQLQ, airway obstruction presented as  $\text{FEV}_1$  %pred. and  $\text{FEV}_1$  to forced vital capacity (FVC) ratio (all  $p > 0.05$ ) between the patients in the VFA<sup>high</sup> and VFA<sup>low</sup> groups. Furthermore, the patients in the VFA<sup>high</sup> group had increased total white blood cells ( $p = 0.038$ ), lymphocytes ( $p = 0.005$ ), and monocytes ( $p = 0.019$ ) but fewer eosinophils ( $p = 0.029$ ) in the blood versus those in the VFA<sup>low</sup> group. For the assessment of airway inflammation, the patients in the VFA<sup>high</sup> group evidently had decreased FeNO ( $p = 0.013$ ) and elevated

sputum IL-6 ( $p = 0.031$ ) and IL-8 ( $p = 0.039$ ) levels, but no difference was found in sputum cells (all  $p > 0.05$ ).

### Correlations of VFA with Clinical and Inflammatory Features

We explored the correlations of VFA with clinical and inflammatory variables (Online Supplemental Tables 1–3). VFA was significantly associated with other variables of body composition, such as BMI ( $r = 0.743$ ,  $p < 0.001$ ), WHR ( $r = 0.479$ ,  $p < 0.001$ ), FM ( $r = 0.943$ ,  $p < 0.001$ ), and PBF ( $r = 0.853$ ,  $p < 0.001$ ). Intriguingly, we found that VFA had gender-differentiated correlations with clinical and inflammatory variables. First, we found that VFA was associated with age ( $r = 0.203$ ,  $p < 0.001$ ; and  $r = 0.307$ ,  $p < 0.001$ ), FeNO ( $r = -0.109$ ,  $p = 0.034$ ; and  $r = -0.145$ ,  $p = 0.025$ ), and IgE ( $r = -0.106$ ,  $p = 0.030$ ; and  $r = -0.120$ ,  $p = 0.050$ ) in either all patients or females, but we failed to find these relationships in male patients. Second, we observed the correlations of VFA with the total number of white cells ( $r = 0.122$ ,  $p = 0.013$ ; and  $r = 0.229$ ,  $p = 0.005$ ) and absolute neutrophils ( $r = 0.107$ ,  $p = 0.029$ ; and  $r = 0.212$ ,  $p = 0.010$ ) in either all patients or males, whereas it did not exist in females. Third, we also found that VFA was associated with sputum levels of IL-1 $\beta$  ( $r = 0.305$ ,  $p = 0.016$ ) and IL-8 ( $r = 0.268$ ,  $p = 0.035$ ) only in males, and blood eosinophils (%) ( $r = -0.098$ ,  $p = 0.045$ ) in all the patients rather than females or males. In addition, we did not find the associations of VFA with ACQ, AQLQ, and airway obstruction as  $\text{FEV}_1$  %pred. and  $\text{FEV}_1/\text{FVC}$  (all  $p > 0.05$ ).

### Asthma Exacerbations

A total of 377 patients (90.4%) who completed the 12-month follow-up were analyzed. It was found that the incidence and frequency of severe

Table 1 Clinical characteristics of patients with asthma grouped by VFA at baseline

| Variable                                               | Low VFA Group<br>(n = 209) | High VFA Group<br>(n = 208) | t/ $\chi^2$ /Z | p      |
|--------------------------------------------------------|----------------------------|-----------------------------|----------------|--------|
| Age, median (Q1, Q 3), y                               | 43.0 (31.5, 54.0)          | 47.0 (38.25, 58.0)          | -3.388         | 0.001  |
| Females/males, n                                       | 125/84                     | 143/65                      | 3.629          | 0.057  |
| Smoking status, current/ex/never, n                    | 19/36/154                  | 21/28/159                   | 1.177          | 0.555  |
| Smoking pack-years, mean $\pm$ SD                      | 5.24 $\pm$ 13.02           | 5.13 $\pm$ 12.52            | -0.530         | 0.596  |
| Atopy, n (%)                                           | 113 (54.1)                 | 107 (51.4)                  | 0.444          | 0.505  |
| Age of asthma onset, median (Q1, Q 3), y               | 32.0 (18.5, 44.0)          | 36.0 (20.25, 47.0)          | -1.351         | 0.177  |
| Asthma duration, median (Q1, Q 3), y                   | 5.0 (2.0, 16.0)            | 7.0 (3.0, 23.0)             | -2.059         | 0.040  |
| ICS, n (%)                                             | 115 (55.0)                 | 123 (59.1)                  | 0.719          | 0.396  |
| ICS dose (BDP equivalent) median (Q1, Q3), $\mu$ g/day | 400 (0, 400)               | 400 (0, 400)                | -0.768         | 0.443  |
| ACQ score, median (Q1, Q3)                             | 0.50 (0.00, 1.33)          | 0.67 (0.04, 1.67)           | -1.217         | 0.223  |
| AQLQ score, median (Q1, Q3)                            | 5.81 (5.08, 6.31)          | 5.59 (5.00, 6.25)           | -1.222         | 0.222  |
| Exacerbation in the past year, n (%)                   | 109 (52.2)                 | 117 (56.3)                  | 0.705          | 0.401  |
| Body composition                                       |                            |                             |                |        |
| BMI, median (Q1, Q3), kg/m <sup>2</sup>                | 20.94 (18.96, 22.34)       | 24.45 (22.83, 26.82)        | -12.830        | <0.001 |
| WHR, median (Q1, Q3)                                   | 0.84 (0.80, 0.89)          | 0.90 (0.86, 0.95)           | -7.780         | <0.001 |
| FM, median (Q1, Q3), kg                                | 12.90 (9.95, 14.80)        | 19.95 (17.53, 23.40)        | -16.303        | <0.001 |
| VFA, median (Q1, Q3), cm <sup>2</sup>                  | 53.40 (42.40, 61.90)       | 95.90 (79.53, 114.78)       | -17.664        | <0.001 |
| PBF, mean $\pm$ SD, %                                  | 23.05 $\pm$ 5.64           | 33.43 $\pm$ 5.60            | -18.854        | <0.001 |
| Comorbidity, n (%)                                     |                            |                             |                |        |
| Rhinitis                                               | 124 (59.3)                 | 106 (51.0)                  | 2.952          | 0.086  |
| Nasal polyps                                           | 23 (11.0)                  | 16 (7.7)                    | 1.349          | 0.245  |
| Gastroesophageal reflux disease                        | 8 (3.8)                    | 13 (6.3)                    | 1.306          | 0.253  |
| Cardiovascular diseases                                | 4 (1.9)                    | 7 (3.4)                     | 0.855          | 0.355  |
| Diabetes                                               | 3 (1.4)                    | 8 (3.8)                     | 2.359          | 0.125  |
| Sleep apnea                                            | 3 (1.4)                    | 1 (0.5)                     | —              | 0.623# |
| Chronic obstructive pulmonary disease                  | 12 (5.7)                   | 14 (6.7)                    | 0.185          | 0.667  |
| Osteoporosis                                           | 4 (1.9)                    | 11 (5.3)                    | 3.423          | 0.064  |
| Spirometry, median (Q1, Q3)                            |                            |                             |                |        |
| FEV <sub>1</sub> , L                                   | 2.21 (1.67, 2.75)          | 1.94 (1.48, 2.49)           | -2.742         | 0.006  |
| FEV <sub>1</sub> , %pred.                              | 76.50 (58.00, 90.00)       | 72.00 (59.00, 86.00)        | -1.039         | 0.299  |
| FVC, L                                                 | 3.30 (2.79, 3.88)          | 2.90 (2.47, 3.59)           | -3.424         | 0.001  |
| FEV <sub>1</sub> /FVC, %                               | 67.17 (56.54, 77.48)       | 67.15 (57.85, 74.69)        | -0.259         | 0.796  |

VFA = Visceral fat area; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation; ICS = inhaled corticosteroid; BDP = beclomethasone dipropionate; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BMI = body mass index; WHR = waist-to-hip ratio; FM = fat mass; PBF = percentage body fat; FEV<sub>1</sub> = forced expiratory volume in 1 second; %pred. = percent predicted; FVC = forced vital capacity.

#p value of the Fisher exact test.

exacerbations were higher in the patients in the VFA<sup>high</sup> group versus the patients in the VFA<sup>low</sup> group (7.4 versus 14.4%,  $p=0.027$ ; and mean  $\pm$  SD 0.13  $\pm$  0.62 versus 0.24  $\pm$  0.76;  $p=0.026$ ). We explored the associations of VFA with asthma exacerbation frequency by negative binomial regression models. As a result, the patients in the VFA<sup>high</sup> group were at significantly increased risk of moderate-to-severe exacerbations (adjusted IRR 1.55 [95% CI, 1.06–2.28];  $p=0.025$ ), severe exacerbations (adjusted IRR 2.25 [95% CI, 1.26–4.04];  $p=0.007$ ), and

emergency visits (adjusted IRR 5.33 [95% CI, 1.78–17.16];  $p=0.003$ ) after adjustment for gender, age, atopy, smoking, asthma duration, ICS dose (beclomethasone dipropionate equivalent) ( $\mu$ g/day) at study baseline and FEV<sub>1</sub> %pred. (Fig. 3).

## DISCUSSION

To the best of our knowledge, few studies explored the association between VFA and asthma, although obesity has been well recognized as an important risk factor that affects asthma control and future risk. In the present study,

**Table 2 The systemic and local inflammatory characteristics of patients with asthma grouped by VFA at baseline**

| Variable                               | Low VFA Group          | High VFA Group         | t/χ <sup>2</sup> /Z | p     |
|----------------------------------------|------------------------|------------------------|---------------------|-------|
| Blood, median (Q1, Q3)                 |                        |                        |                     |       |
| Total white cells, ×10 <sup>9</sup> /L | 5.69 (4.68, 6.79)      | 6.09 (5.03, 7.43)      | -2.079              | 0.038 |
| Neutrophils                            |                        |                        |                     |       |
| ×10 <sup>9</sup> /L                    | 3.39 (2.62, 4.30)      | 3.57 (2.81, 4.51)      | -1.647              | 0.099 |
| %*                                     | 59.46 ± 9.12           | 59.59 ± 8.54           | -0.154              | 0.878 |
| Eosinophils                            |                        |                        |                     |       |
| ×10 <sup>9</sup> /L                    | 0.25 (0.12, 0.40)      | 0.20 (0.11, 0.36)      | -1.185              | 0.236 |
| %                                      | 4.30 (2.42, 6.43)      | 3.25 (2.04, 6.14)      | -2.187              | 0.029 |
| Lymphocytes                            |                        |                        |                     |       |
| ×10 <sup>9</sup> /L                    | 1.62 (1.35, 1.93)      | 1.74 (1.45, 2.07)      | -2.822              | 0.005 |
| %*                                     | 28.75 ± 7.44           | 29.22 ± 6.93           | -0.669              | 0.504 |
| Monocytes                              |                        |                        |                     |       |
| ×10 <sup>9</sup> /L                    | 0.34 (0.26, 0.43)      | 0.36 (0.29, 0.46)      | -2.353              | 0.019 |
| %                                      | 0.06 (0.05, 0.07)      | 0.06 (0.05, 0.07)      | -1.000              | 0.317 |
| Basophils                              |                        |                        |                     |       |
| ×10 <sup>9</sup> /L                    | 0.03 (0.02, 0.05)      | 0.04 (0.02, 0.05)      | -0.625              | 0.532 |
| %                                      | 0.01 (0.00, 0.01)      | 0.01 (0.00, 0.01)      | -0.350              | 0.726 |
| IgE level, IU/mL                       | 155.50 (43.53, 360.50) | 119.71 (43.10, 234.76) | -1.899              | 0.058 |
| Sputum, median (Q1, Q3)                |                        |                        |                     |       |
| Total cells, ×10 <sup>6</sup> /mL      | 0.30 (0.12, 0.52)      | 0.26 (0.15, 0.51)      | -0.017              | 0.987 |
| Neutrophils                            |                        |                        |                     |       |
| %                                      | 35.75 (15.50, 67.75)   | 38.50 (15.50, 68.25)   | -0.207              | 0.836 |
| ×10 <sup>4</sup> /mL                   | 8.42 (2.45, 28.83)     | 9.34 (2.07, 31.64)     | -0.154              | 0.878 |
| Eosinophils                            |                        |                        |                     |       |
| %                                      | 0.25 (0.00, 3.00)      | 0.25 (0.00, 2.75)      | -0.488              | 0.625 |
| ×10 <sup>4</sup> /mL                   | 0.08 (0.00, 1.29)      | 0.07 (0.00, 0.61)      | -0.501              | 0.617 |
| Lymphocytes                            |                        |                        |                     |       |
| %                                      | 0.50 (0.00, 1.25)      | 0.50 (0.25, 1.50)      | -1.402              | 0.162 |
| ×10 <sup>4</sup> /mL                   | 0.14 (0.00, 0.40)      | 0.19 (0.04, 0.37)      | -1.227              | 0.220 |
| Macrophages                            |                        |                        |                     |       |
| %                                      | 50.00 (22.25, 77.75)   | 46.50 (21.00, 75.25)   | -0.171              | 0.865 |
| ×10 <sup>4</sup> /mL                   | 11.42 (3.83, 18.14)    | 10.54 (4.46, 20.09)    | -0.177              | 0.860 |
| FeNO, median (Q1, Q3), ppb             | 43.00 (22.00, 90.00)   | 30.00 (18.00, 63.25)   | -2.479              | 0.013 |

VFA = Visceral fat area; Q1 = quartile 1; Q3 = quartile 3; IgE = immunoglobulin E; FeNO = Fractional exhaled nitric oxide.

\*Data are presented as mean ± standard deviation.

the patients with an elevated VFA were found to be older, have longer asthma duration, have elevated total white blood cells and fewer eosinophils as systemic inflammation biomarkers, and decreased FeNO and increased sputum IL-6 and IL-8 as local inflammation biomarkers but no difference in ACQ, AQLQ, and airway obstruction. Intriguingly, correlations of VFA with clinical and inflammatory variables were gender specific. Furthermore, our negative binomial regression models indicated that the patients in the VFA<sup>high</sup> group were at increased risk of moderate-to-severe exacerbations, severe exacerbations, and emergency visits. Analysis of the results of our study suggested that VFA would provide more potential clinical implications for asthma management.

This study found that, regardless of gender, VFA showed a strong positive correlation with FM, PBF, and BMI, but the correlation coefficient of BMI with VFA was lower than that of FM and PBF. Furthermore, VFA showed a moderate positive correlation with WHR. Accordingly, it indicated that BMI and WHR cannot accurately reflect VFA. General obesity and central obesity can be easily diagnosed by the measurement of BMI and WHR or WC, respectively. However, although these indicators are easy to measure and frequently used, they cannot distinguish lean tissue from body fat or distinguish differences between subcutaneous and visceral fat compartments.<sup>33</sup> When compared with BMI and WHR by anthropometric measurements, VFA by bioelectrical

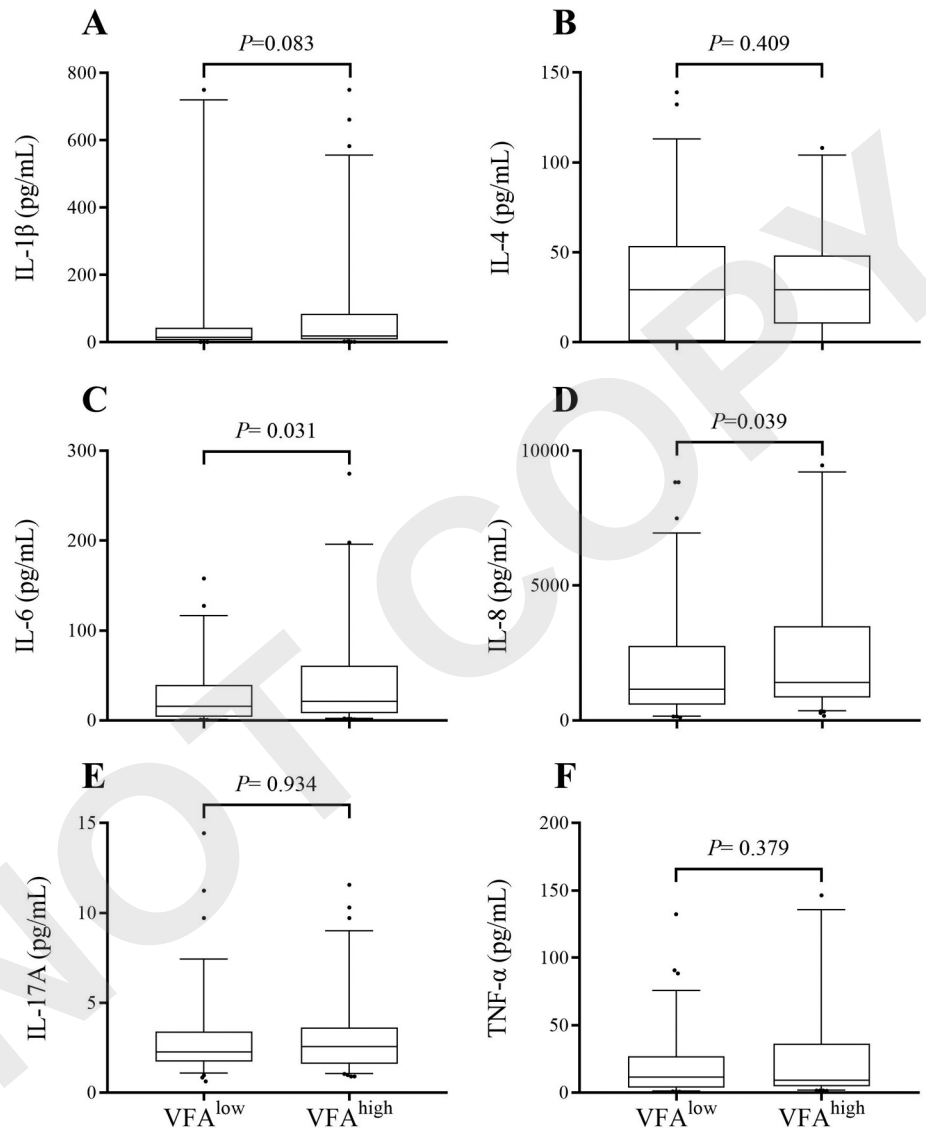


**Figure 2.** The levels of (A) IL-1 $\beta$ , (B) IL-4, (C) IL-6, (D) IL-8, (E) IL-17A, and (F) TNF- $\alpha$  in induced sputum from the patient in the low VFA (VFA<sup>low</sup>) and high VFA (VFA<sup>high</sup>) groups. The horizontal line in the box indicates the median value, the box indicates interquartile range, and the vertical lines indicate the 5 to 95 percentile. IL = Interleukin; TNF = tumor necrosis factor; VFA = visceral fat area.

impedance analysis had several advantages as follows. First, VFA had the best correlation with computed tomography measurement.<sup>34</sup> Second, VFA showed a linear association with morbidity and mortality rather than a U-shaped association when using BMI.<sup>35</sup> Third, the measurement of VFA by bioimpedance is practical; cost effective; and safe, without radiation exposure.<sup>33</sup> Therefore, VFA may be a better marker of obesity that influences asthma than BMI or WHR. Our study found that VFA was significantly associated with age in the female rather than the male patients. This was consistent with the observation that visceral fat accumulates with age.<sup>36,37</sup> Furthermore, Hunter *et al.*<sup>36</sup> found that VFA increases with age were dramatic in the female patients. It could be explained by gonadal hormones decline with age, which resulted in increased visceral fat, especially during menopause in females.<sup>38-40</sup>

Previous studies by Goudarzi *et al.*<sup>14</sup> and us<sup>41</sup> explored the impact of VFA on adult asthma

symptoms. As a result, we found that there was a significant difference in ACQ scores ( $p=0.002$ ) rather than AQLQ scores ( $p=0.093$ ) in patients grouped by BMI category, and VAF was significantly associated with ACQ-6 ( $\beta=0.012$ ,  $p=0.035$ ).<sup>41</sup> Goudarzi *et al.*<sup>14</sup> further found that, regardless of gender, VFA was inversely associated with reduced AQLQ score, which may be explained by the impact of abdominal visceral fat on reduced FEV<sub>1</sub> %pred. and a higher risk for gastroesophageal reflux disease and depression. However, our present study did not find any relationships between VFA and ACQ or AQLQ scores, which was not consistent with the findings from these previous studies.<sup>14,41</sup>

There are some issues that can explain these different findings as follows. First, there was a lower proportion of patients with severe asthma (15.11 versus 61.6%) and decreased obesity status (mean  $\pm$  SD 23.01  $\pm$  3.57 versus 24.9  $\pm$  5.0 kg/m<sup>2</sup>) in our study versus subjects in the study by Goudarzi *et al.*,<sup>14</sup> which would reduce the

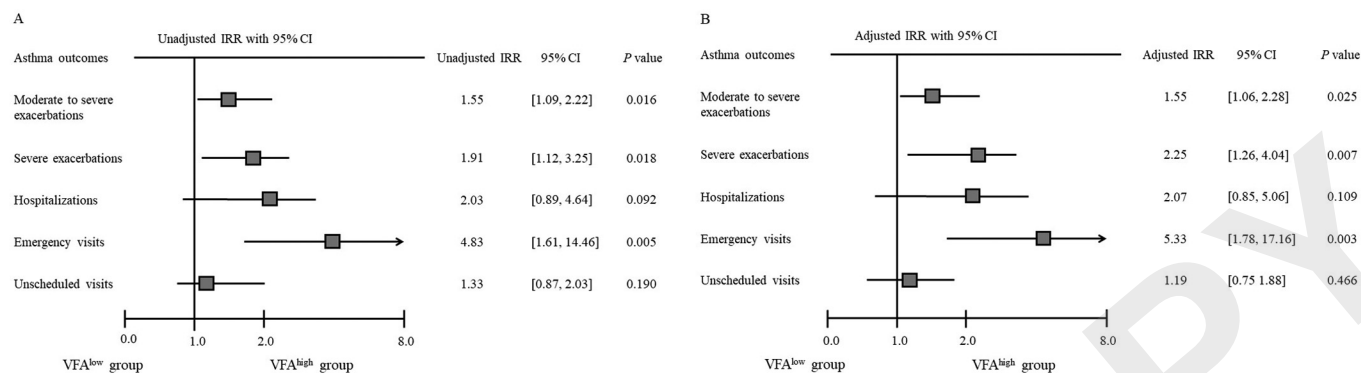


**Figure 3.** Forest plot of  $VFA^{low/high}$  in predicting asthma exacerbations within the 12-month follow-up period analyzed by negative binomial regression models; (A) unadjusted models; (B) adjusted models, adjusted for gender, age, atopy, smoking, asthma duration, ICS dose (BDP equivalent [ $\mu\text{g/day}$ ]) at the study baseline and the  $FEV_1$  %pred. VFA = visceral fat area; IRR = incidence rate ratio; CI = confidence interval;  $FEV_1$  = forced expiratory volume in 1 second; pred. = predicted; ICS = inhaled corticosteroid; BDP = beclomethasone dipropionate.

contribution of obesity status to asthma symptoms. Second, some subjects may not have been optimally controlled, which would confound the symptom data. In the study by Goudarzi *et al.*,<sup>14</sup> 61.6% of the subjects were of severe asthma (Global Initiative for Asthma (GINA) step 4 or 5 treatment), 21.8% used maintenance oral corticosteroids. However, almost all of the subjects (94.4%) were ICS or oral corticosteroid naive in our previous study,<sup>41</sup> which indicated that most of the patients with more asthma symptoms were of undertreatment. In this study, 57.1% of the subjects in a real-world setting received maintenance of ICS. Third, the AQLQ consisted of four sections, including symptoms, activity limitations, emotional function, and exposure to environmental stimuli.<sup>14,30</sup> Emotional function, *e.g.*, depression, has been reported to have a mediator effect on the association between obesity and asthma control.<sup>42</sup> Therefore, the association between VFA and AQLQ scores found in the study by Goudarzi *et al.*<sup>14</sup> may reflect a relationship between VFA and depression rather than asthma symptoms, especially in patients with severe asthma. Due to differences in the cohorts, there may not be an emotion-induced connection between VFA and asthma control in our population.

In this study, comparable airway obstruction was found in  $FEV_1$  %pred. and  $FEV_1$ /FVC between the  $VFA^{high}$  and  $VFA^{low}$  groups. The effect of obesity on airway obstruction in asthma is controversial.<sup>3</sup> Some studies observed an association between obesity (assessed by using BMI) and  $FEV_1$  %pred. or  $FEV_1$ /FVC,<sup>43–45</sup> but other studies did not.<sup>46,47</sup> In addition, a recently published study reported that VFA, but neither BMI nor WC, had a significantly inverse association with  $FEV_1$  %pred.<sup>14</sup> Accordingly, the possible issues that account for these discrepant observations need to be explored in further studies.

Visceral adipose tissue is an active endocrine organ that produces proinflammatory cytokines that regulate immune responses.<sup>48</sup> These various proinflammatory cytokines, including tumor necrosis factor  $\alpha$  and IL-6, could lead to the systemic complications of obesity and augment airway inflammation, producing asthma in obesity. In this study, compared with the  $VFA^{low}$  group, the  $VFA^{high}$  group exhibited a low type 2 (T2) driven inflammation with decreased FeNO and blood eosinophils levels, and elevated sputum IL-6 and IL-8 levels. This corresponded well with previously published studies.<sup>49,50</sup>

Interestingly, the correlations of VFA with systemic and airway inflammation were different in females from males. For example, VFA negatively linked to T2 inflammatory biomarkers, such as FeNO and IgE, in females, whereas in males VFA were linked to increased non-T2 inflammatory biomarkers, such as the total white blood cells and absolute neutrophils in blood and sputum IL-1 $\beta$  and IL-8. As indicated by Scott *et al.*,<sup>49</sup> sexual dimorphism in body composition could lead to distinct differences in the inflammatory pattern. In addition, sex hormones could affect the immune response, with progesterone antagonizing the T1 response and promoting the T2 response.<sup>51,52</sup> Females with obesity and with decreased circulating progesterone, and elevated oestradiol could cause different inflammation characteristics in males.<sup>53,54</sup> However, the relevant mechanisms require further study.

By evaluating the relationship between VFA and asthma outcomes, we found that patients with a high level of VFA had an increased risk of asthma exacerbations. This result was consistent with finding that those who are obese and with asthma had greater exacerbation rates.<sup>55</sup> There were some issues that would account for this result. First, although there was no difference in the proportion of patients with severe asthma (GINA step 4 or 5 treatment) between the  $VFA^{high}$  and  $VFA^{low}$  groups, the

VFA<sup>high</sup> group had a higher proportion of severe patients with ACQ scores  $\geq 1.5$  than those in the VFA<sup>low</sup> group (38.8 versus 11.6%;  $p=0.003$ ), which indicated that the patients with uncontrolled severe asthma in the VFA<sup>high</sup> group were prone to have more severe asthma exacerbations in the following 12-month period. Second, the VFA<sup>high</sup> group had a lower FeNO level and a reduction of eosinophils in their blood, which may indicate less response to anti-asthma therapies such as corticosteroids and montelukast.<sup>56,57</sup> Third, there was elevated local non-T2 inflammation, such as IL-6 and IL-8, in the VFA<sup>high</sup> group, which was indicative of glucocorticoid resistance.<sup>58,59</sup> However, there was no difference in asthma exacerbations in the past year; the possible reason was that patients had poorer adherence, there was undertreatment, and inadequate management before entering the study, which may have weakened the associations of VFA with asthma exacerbations. In addition, the study by Goudarzi *et al.*<sup>14</sup> did not support our findings, which could be explained by patients who were not obese or who had low VFA with severe asthma at increased risk of exacerbation.

In the current study, to explore whether the correlations between VFA and clinical and inflammatory features of asthma, is independent of obesity, we re-analyzed the correlations between VFA and clinical and inflammatory features of asthma after adjustment of obesity. As a result, we found almost all results unchanged except for the correlations of VFA with leukocytes, neutrophils, and IL-8 (Online Supplemental Tables 4–7), which indicated that VFA had an efficacy independent of obesity to some extent. Thus, we should not only focus on obesity but also VFA for the personalized management and precision-based care of patients with asthma.<sup>60–62</sup>

This study had some limitations. First, VFA was measured only once, at the baseline, although VFA had been reported to change relatively little after 3 years.<sup>63</sup> Second, medication exposure for these included patients within the 12-month period were not analyzed in the VFA<sup>low</sup> and VFA<sup>high</sup> groups, although this was a prospective, real-world, noninterventional, observational study. Third, inflammatory markers of asthma were measured only once, at the baseline. Therefore, it may not be representative of how inflammatory markers may have changed during the course of the 12-month follow-up period.

## CONCLUSION

This study identified that patients with elevated VFA levels were characterized as being older, having a longer asthma duration, and having elevated total white blood cells and fewer eosinophils as systemic inflammation biomarkers; and decreased FeNO and increased sputum IL-6 and IL-8 as local inflammation biomarkers. Gender-differentiated correlations of VFA

with clinical and inflammatory variables were observed in age, FeNO, IgE levels, blood total white cells and neutrophils, and sputum IL-1 $\beta$  and IL-8 values. Furthermore, patients in the VFA<sup>high</sup> group were at increased risk of moderate-to-severe exacerbations, severe exacerbations, and emergency visits. Results of our study suggested that VFA would provide more potential clinical implications for asthma management.

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