ORIGINAL RESEARCH

Andréa Lessard MSc
Nathalie Alméras PhD
Hélène Turcotte MSc
Angelo Tremblay PhD
Jean-Pierre Després PhD, FAHA
Louis-Philippe Boulet MD, FRCPC

Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec (CRIUCPQ), Québec, Canada.

Adiposity and pulmonary function: Relationship with body fat distribution and systemic inflammation

Abstract

Purpose: Obesity is associated with changes in pulmonary function and increased systemic inflammation. We explored the relationships among adiposity, body fat distribution indices, serum inflammatory markers and pulmonary function.

Methods: This was a post-hoc cross-sectional analysis that included subjects who had previously participated in randomized studies on obesity at our centre. Non-smoking sedentary men (282 subjects, mean age 42) without respiratory diseases were studied. BMI, waist circumference (WC), visceral and subcutaneous adipose tissue (AT), lung residual volume (RV), vital capacity (VC) and expiratory reserve volume (ERV) were measured. Serum leptin, adiponectin, tumor necrosis factor alpha (TNF-α) and high-sensitive C-reactive protein (hs-CRP) levels were measured.

Results: In subjects with metabolic syndrome (n=124), percent predicted ERV and RV were significantly associated with BMI (ERV: r=-0.19, p=0.02, RV: r=-0.28, p=0.0007), WC (r=-0.20, p=0.02, r=-0.26, p=0.002), visceral (r=-0.22, p=0.007, r=-0.25, p=0.002) and subcutaneous AT (r=-0.19, p=0.02, r=-0.28, p=0.0007). Percent predicted VC correlated with visceral (r=-0.20, p=0.02) and subcutaneous AT (r=-0.18, p=0.03). Leptin was strongly correlated with BMI (MS/no-MS: r=0.52, p=0.0005/r=0.62, p<0.0001), WC (r=0.41, p=0.008/r=0.49, p<0.0001), visceral (r=0.27,p=0.09/0.43, p<0.0001) and subcutaneous AT (r=0.46, p=0.003/r=0.66, p<0.0001), while adiponectin levels were associated in subjects with no-MS with WC (r=-0.20, p=0.01), visceral (r=-0.22, p=0.008), and subcutaneous AT (r=-0.17, p=0.05). When adjusted for anthropometric measures, neither ERV, RV nor VC was significantly correlated with serum leptin, adiponectin, TNF-α, or hs-CRP levels.

Conclusion: These results suggest that the influence of obesity on lung function in healthy subjects is mostly mediated by mechanical factors. Furthermore, not only BMI but also the pattern of fat distribution should be considered when studying associations between adiposity indices and mechanical or inflammatory variables potentially associated with pulmonary function.

Manuscript submitted 28th September, 2010
Manuscript accepted 8th March, 2011

Clin Invest Med 2011; 34 (2): E64-E70.

Correspondence to:
Louis-Philippe Boulet, MD
Institut universitaire de cardiologie et de pneumologie de Québec (IUCPQ)
2725 chemin Sainte-Foy, Québec, QC Canada, G1V 4G5
Email: lpboulet@med.ulaval.ca

Obesity is associated with an increase in the work of breathing, reduced respiratory compliance and hypoventilation, and has been considered to contribute to disorders such as sleep apnea syndrome, obesity/hyperventilation syndrome and, more recently, asthma [1]. Increased body mass index (BMI) is also associated with lung mechanical changes such as reduced functional residual capacity (FRC) and expiratory reserve volume (ERV). It has been suggested that pulmonary function could be influenced by body fat distribution as assessed by the ratio of waist-to-hip circumferences [2,3]; however, waist-to-hip ratio provides only an index of relative accumulation of abdominal fat [4]. There is a need to study the impact of abdominal fat distribution, assessed by more precise imaging techniques such as computed tomography, on pulmonary function.

Obesity is an inflammatory state. Among others, serum leptin levels, a pro-inflammatory adipokine and serum levels of TNF-α are increased in obesity [5]. Consistent with this, serum adiponectin level, an anti-inflammatory adipokine, is typically decreased in the obese subject [5]. These hormones have been suggested to play a role in the pathogenesis of cardiovascular diseases and diabetes [6]. Plasma IL-6, C-reactive protein (CRP) and TNF-α are inflammatory factors that are also increased in obesity [7-9]. Therefore, the systemic inflammation associated with obesity could contribute to the development and/or the persistence of airway inflammatory disorders such as asthma and Chronic Pulmonary Obstructive Disease (COPD) [10,11]. The additional impact on pulmonary function of systemic inflammation, and their relationships with mechanical changes associated with obesity, remains to be determined.

The main objective of this study was to quantify the relationships among anthropometric markers of adiposity/body fat distribution and specific variations in pulmonary function in subjects with and without a metabolic syndrome (MS or no-MS). As secondary analyses, the relationships between anthropometric markers and systemic inflammatory factors were compared and the links between markers of systemic inflammation and pulmonary function were evaluated.

Materials and Methods

This post-hoc cross-sectional analysis was conducted on a database kept in our institution that included male subjects who had previously taken part in randomized studies on obesity and for whom data on pulmonary function was available. Various markers of obesity and systemic inflammation were measured in a sub-group of this cohort, in the context of a research program on the metabolic effects of obesity. All subjects were sedentary, doing less than 30 minutes of exercise per week, aged 18 years and over, had no known metabolic disorders or respiratory diseases and were non-smokers at the time of the enrolment. All appropriate subjects were included in the study. The studies were approved by the Ethics Committee of Laval Hospital Research Center and all subjects had signed an informed consent form.

Body mass index (BMI) was calculated from measured height and weight. Obesity, was defined as a BMI $\geq$30 kg/m^2, overweight $\geq$25 to <30 kg/m^2 and normal weight <25 kg/m^2. Waist circumference (WC) was measured at the narrowest part of the torso while the subject was standing. Abdominal visceral and subcutaneous adipose tissue (AT) area were measured by computed tomography (CT) on a Siemens Somatom DRH scanner (Erlangen, Germany) as previously described [12].

FRC was assessed with the helium dilution technique of Meneely and Kaltreider [13]. ERV was calculated by subtracting VC from FRC. Residual volume (RV) was obtained in subtracting ERV from FRC. Pulmonary volumes were expressed as percentage of predicted values. Predicted values were calculated using reference values of the European Respiratory Society [14].

Blood samples were obtained in the morning after a 12h overnight fast. Fasting plasma leptin and adiponectin concentrations were determined by an enzyme-linked immunosorbent assay (ELISA) (B-Bridge International, Inc., San Jose, CA, USA) on whole plasma kept at –80°C until use. Fasting plasma tumor necrosis factor alpha (TNF-α) concentrations were also assessed on deeply frozen plasma samples (80°C) and were measured by a high sensitivity ELISA for human TNF-α (R&D Systems Inc, Minneapolis, USA). Serum IL-6 levels were measured using a human IL-6 Elisa kit (R&D Systems Inc, MN, USA). High sensitive-CRP (hs-CRP) was assessed using a highly sensitive immunoassay (hs-CRP) that uses a monoclonal antibody coated to polystyrene particles performed on the Behring BN-Prospect nephelometer (Dade Behring) according to methods described by the manufacturer [15].

The criteria used to define metabolic syndrome (MS) were those of the Diabetes International Federation; that is to have at least three of the five following risk factors: high fasting plasma glucose (>5.6 mmol/L), high blood pressure (≥ 130/85 mmHg), increased waist circumference (≥ 102 cm), increased triglycerides (≥ 1.7 mmol/L) and reduced HDL-cholesterol (≤ 1.0 mmol/l) [16].

Variables were expressed using mean ± standard deviation. Relationships between variables were measured using univariate linear regression analyses. To take into account possible confounding factors, such as BMI, WC and AT, adjusted corre-

TABLE 1. Subject's characteristics

	Metabolic syndrome (n=124)	No metabolic syndrome (n = 158)	p
Age, yr	44± 8	41 ± 10	0.02
BMI (kg/m^2)	32 ± 3	26 ± 4	<0.0001
WC (cm)	108 ± 8	91 ± 11	<0.0001
Visceral AT (cm^2)	203 ± 59	123 ± 57	<0.0001
Subcutaneous AT(cm^2)	326 ± 90	215 ± 109	<0.0001

BMI: body mass index; WC: waist circumference; AT: adipose tissue
Mean ± SD

lations were performed using multivariate regression analyses. P-value < 0.05 using a two-tailed test was deemed significant. Data were analysed using the statistical package SAS (SAS Institute, Inc.,Cary, NC, USA).

Results

Two hundred eighty two men were included in the analysis. A total of 124 subjects responded to the criteria of a MS while the other 158 had no-MS, with fewer than three metabolic risk factors. Many subjects had measures of systemic inflammatory factors such as leptin (n = 132), adiponectin (n = 267), TNF-α (n = 228), IL-6 (n = 228), hs-CRP (n = 91) and white blood cell (WBC) count (n = 205). The subjects' characteristics are summarized in Table 1. BMI distribution is presented in Figure 1.

Among the MS and no-MS subjects, mean percent of predicted ERV was, respectively, 85 ± 47 and 96 ± 33 (p = 0.02), mean percent of predicted values were, respectively, 90 ± 20 and 91 ± 17 (p = 0.60) for RV, 98 ± 11 and 101 ± 12 (p = 0.009) for VC, and 79 ± 16 and 96 ± 21 (p < 0.0001) for FRC. Correlations between anthropometric measurements and specific variations in pulmonary function are presented in Table 2. Briefly, in subjects with a MS, decreased percent of predicted ERV and RV were significantly associated with an increased BMI, WC, visceral and subcutaneous AT. Decreased percent of predicted VC was only slightly but significantly correlated with visceral and subcutaneous AT although not with BMI and WC. There were no significant correlations between anthropometric measurements and percent of predicted ERV, RV or VC in subjects with no-MS.

Mean values for measured inflammatory markers are given in Table 3 for subjects with or without MS. Leptin, adiponeptin and hs-CRP levels and WBC counts were significantly higher in subjects with MS than in those with no-MS. Among the subjects with a MS who had systemic inflammatory marker measurements, leptin was significantly correlated with BMI, WC, and subcutaneous AT while adiponectin, Il-6 and TNF-α were not significantly correlated with any of the anthropometric markers. Hs-CRP was significantly correlated with WC and

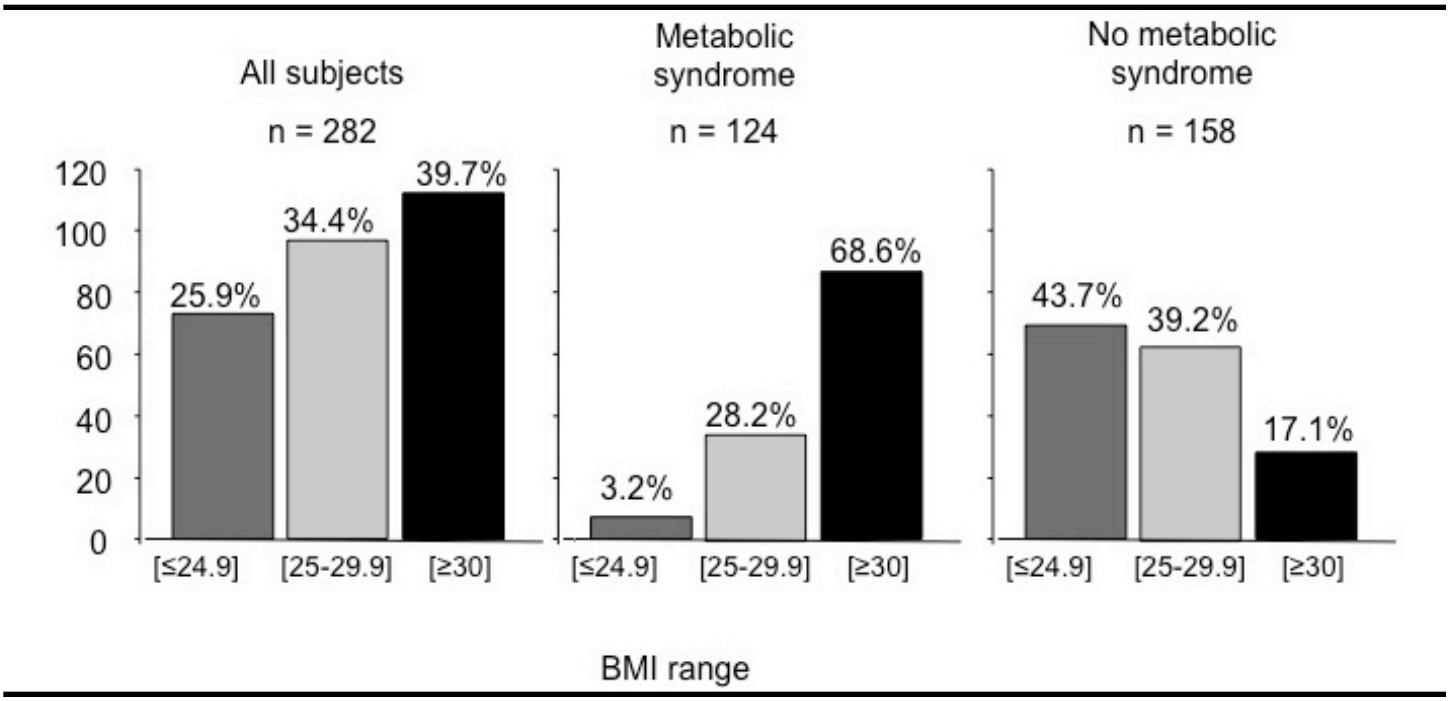

FIGURE 1. BMI distribution in the 282 subjects with (n = 124) or without (n = 158) metabolic syndrome

TABLE 2. Correlations between anthropometric measurements and lung volumes

	BMI		WC		Visceral AT		Subcutaneous AT	
	r	p	r	p	r	p	r	p
Metabolic syndrome								
% of predicted ERV	-0.19	0.02	-0.20	0.02	-0.22	0.007	-0.19	0.02
% of predicted RV	-0.28	0.0007	-0.26	0.002	-0.25	0.002	-0.28	0.0007
% of predicted VC	-0.11	0.19	-0.13	0.11	-0.20	0.02	-0.18	0.03
No metabolic syndrome								
% of predicted ERV	-0.03	0.77	0.09	0.30	0.13	0.14	0.006	0.95
% of predicted RV	-0.002	0.98	0.14	0.12	0.08	0.40	0.07	0.44
% of predicted VC	0.06	0.53	0.02	0.84	-0.15	0.09	-0.02	0.85

BMI: body mass index; WC: waist circumference; AT: adipose tissue; TNF-alpha: tumor necrosis factor; IL-6: Interleukine-6; Hs-CRP: high-sensitive C-reactive protein; WBC: white blood cells.

TABLE 3. Lung volumes and systemic inflammatory factors measurements

Systemic inflammatory factors:	Metabolic syndrome	No metabolic syndrome	p
Leptin (ng/ml)	12.5 ± 9.5	6.6 ± 6.9	<0.0001
Adiponectin (µg/ml)	8.4 ± 3.8	9.9 ± 5.7	0.02
TNF-alpha (pg/ml)	1.4 ± 0.7	1.2 ± 0.6	0.07
IL-6 (pg/ml)	1.3 ± 0.9	1.1 ± 1.1	0.20
Hs-CRP (mg/L)	1.8 ± 1.2	0.9 ± 0.9	0.0005
WBC (X 10^9/L)	6.0 ± 1.1	5.5 ± 1.3	0.003

ERV: expiratory reserve volume; RV: residual volume; VC: vital capacity; TNF-alpha: Tumor necrosis factor; IL-6: Interleukine-6; Hs-CRP: High-sensitive C-reactive protein; WBC: white blood cells.
Mean ± SD

TABLE 4. Correlations between systemic inflammatory factors and anthropometric measurements

	BMI		WC		Visceral AT		Subcutaneous AT	
	r	p	r	p	r	p	r	p
Metabolic syndrome								
Leptin (n = 41)	0.52	0.0005	0.41	0.008	0.27	0.09	0.46	0.003
Adiponectin (n = 121)	0.47	0.61	0.08	0.39	-0.05	0.61	0.15	0.11
TNF-alpha (n = 107)	0.03	0.76	0.04	0.69	0.06	0.57	0.06	0.53
IL-6 (n = 108)	0.14	0.15	0.11	0.24	0.08	0.43	0.09	0.33
Hs-CRP (n = 20)	0.37	0.11	0.52	0.02	0.51	0.02	0.41	0.08
WBC (n = 102)	0.16	0.11	0.26	0.007	0.18	0.08	0.15	0.13
No metabolic syndrome								
Leptin (n = 91)	0.62	<0.0001	0.49	<0.0001	0.43	<0.0001	0.66	<0.0001
Adiponectin (n = 146)	-0.16	0.06	-0.20	0.01	-0.22	0.008	-0.17	0.05
TNF-alpha (n = 121)	0.05	0.60	0.02	0.82	-0.02	0.87	0.10	0.30
IL-6 (n = 120)	0.21	0.02	0.16	0.07	0.09	0.35	0.23	0.01
Hs-CRP (n = 71)	0.26	0.03	0.26	0.03	0.19	0.12	0.25	0.04
WBC (n = 103)	0.21	0.04	0.24	0.02	0.23	0.02	0.24	0.01

BMI: body mass index; WC: waist circumference; AT: adipose tissue; TNF-alpha: tumor necrosis factor; IL-6: Interleukine-6; Hs-CRP: high-sensitive C-reactive protein; WBC: white blood cells.

TABLE 5. Correlations between systemic inflammatory factors and lung volumes adjusted for anthropometric measurements

	% of predicted ERV		% of predicted RV		% of predicted VC	
	r	p	r	p	r	p
Metabolic syndrome						
Leptin (n = 41)	0.15	0.36	-0.05	0.78	-0.15	0.34
Adiponectin (n = 121)	0.17	0.07	0.12	0.18	0.11	0.22
TNF-alpha (n = 107)	-0.11	0.25	0.002	0.99	-0.07	0.50
IL-6 (n = 108)	-0.04	0.65	-0.05	0.61	-0.08	0.44
Hs-CRP (n = 20)	-0.16	0.49	0.32	0.17	-0.11	0.63
WBC (n = 102)	-0.13	0.20	0.11	0.28	-0.18	0.07
No metabolic syndrome						
Leptin (n = 91)	-0.02	0.83	-0.19	0.08	-0.07	0.07
Adiponectin (n = 146)	0.11	0.20	0.11	0.17	0.06	0.50
TNF-alpha (n = 121)	0.08	0.40	0.04	0.69	0.0006	0.99
IL-6 (n = 120)	-0.17	0.06	0.05	0.62	-0.23	0.01
Hs-CRP (n = 71)	-0.10	0.40	-0.06	0.61	0.11	0.38
WBC (n = 103)	-0.12	0.24	-0.16	0.10	-0.20	0.05

ERV: expiratory reserve volume; RV: residual volume; VC: vital capacity; TNF: tumor necrosis alpha; Hs-CRP: high-sensitive C-reactive protein; WBC: white blood cells; IL-6: interleukine-6.

visceral AT and WBC were significantly correlated with WC only (Table 4). In subjects without MS, leptin was strongly correlated with increased BMI, WC, visceral and subcutaneous AT, adiponectin was significantly correlated with WC, visceral AT and also slightly with subcutaneous AT. IL-6, hs-CRP and WBC were significantly but slightly correlated with BMI and subcutaneous AT, hs-CRP and WBC were also slightly correlated with WC and finally, WBC was slightly correlated with visceral AT (Table 4).

Finally, when adjusted for BMI, WC, visceral and subcutaneous AT, neither ERV, neither RV nor VC were correlated with leptin, adiponectin, TNF-α or hs-CRP in either subjects with MS or without MS (Table 5). No significant correlations were found between IL-6 or WBC and ERV, RV or VC in subjects with MS. A weak correlation was found in subjects with no-MS between VC and IL-6 and between VC and WBC.

Discussion

We found that ERV, RV and leptin levels are significantly associated with anthropometric measures in subjects with MS while there are no significant associations among ERV, RV or VC and anthropometric measures subjects without MS. Furthermore, leptin and adiponectin levels are significantly correlated with anthropometric measures in subjects with no MS. Markers of systemic inflammation were not significantly associated with changes in ERV, RV and VC after adjustment for anthropometric characteristics except for a weak correlation of IL-6 and WBC with changes in VC in subjects with no-MS.

Our study suggests that the obesity phenotype, in terms of fat distribution, should be taken into consideration when evaluating the impact of obesity on pulmonary function. As already reported, increased BMI is associated with a reduction in ERV often without change in RV [1]. In agreement with recent data from Babb *et al.,* correlations among markers of abdominal obesity and ERV were similar to those with BMI, suggesting that global obesity rather than abdominal obesity *per se* is associated with breathing near the closing volume [17]; however, a different conclusion was reached for VC. While a study by Ray *et al.* showed no change in VC among 43 healthy non-smoking obese subjects [18], VC was reduced to 75% of the predicted value in 43 morbidly obese subjects [19]. In our study, the correlation was significant with visceral and subcutaneous AT in subjects with MS, suggesting that body fat distribution may particularly influence VC in this group. Since ERV seems to be influenced by BMI and not only abdominal obesity, these results suggest an impact of abdominal obesity on inspiratory capacity. It has been suggested that decreased inspiratory capacity in obese subjects may result in impaired inspiratory muscle activity during exercise [20] and in reduction of the bronchoprotection of deep inspiration during induced bronchoconstriction [21]. The impact of body mass distribution on inspiratory capacity and its link to dyspnea and respiratory diseases such asthma in obese subjects needs to be further explored.

As already reported in other studies, serum levels of adiponectin seemed to be influenced by the body mass distribution. In agreement with Staiger *et al.* [5], adiponectin levels were found to be predominantly related to the visceral fat compartment while serum leptin levels were associated with overall obesity as estimated by the BMI. Since adipokines have been proposed to play a role in the physiopathology of respiratory diseases in obese subjects [10,11], these results reiterate the importance of considering body fat distribution when assessing pulmonary function in obese subjects.

Finally, there were no significant association between most of the systemic inflammatory markers classically associated with obesity and pulmonary function changes, suggesting that the impact of obesity on pulmonary function is mainly mediated by mechanical factors. Little is known about the effect of systemic inflammation markers on pulmonary function among subjects without known respiratory disease and this study provides additional data on this topic.

This study has some limitations, being a retrospective analysis performed only on data from male subjects with markers of inflammation assessed only in sub-groups of subjects. Nevertheless, highly significant results were obtained, shedding more light on the combined effects of mechanical and inflammatory markers on pulmonary function of the obese subject. Our study is also limited to lung volumes and the effects of the factors evaluated on airway obstruction could not be evaluated. Such analysis should be performed in subjects with airway inflammatory diseases to determine if similar associations would be observed. Sutherland *et al.* recently suggested that systemic inflammation does not significantly influence airway inflammation in obese asthmatic subjects, although this issue will require more extensive evaluation [22]. Watz *et al.* showed that about half of the patients with chronic bronchitis and COPD had a co-existing metabolic syndrome associated with increased level of hs-CRP and IL-6 independent of lung function impairment [23]. An inverse relationship has also been shown between CRP concentrations and measures of pulmonary function (FEV_1, FVC and PEF) in subjects without pulmonary diseases and in non-smokers [24]. Kony *et al.* found that in adults, increased CRP levels were strongly and independently associated with FEV_1 and FVC impairment and more frequent bronchial hyperresponsiveness [25] and that both female gender and CRP levels were significantly associated with airway hyperresponsiveness. Our study included men only and different lung volumes were evaluated; these differences could explain some apparent discrepancies between the results. Rasmussen *et al.* showed that in young men, higher levels of CRP at age 20 years predicted the decline in lung function by age 39 years [26]; however, other studies either on young or older adults did not demonstrate that CRP levels predicted a subsequent decline in lung function [27,28].

It is possible that lung function could be altered by other obesity-associated features such as the metabolic syndrome. In our study, a significant inverse correlation was found between lung function measures (ERV and RV) and BMI, WC, visceral and subcutaneous tissue only in the group of subject with metabolic syndrome. Indeed, this last syndrome, usually characterized by abdominal obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and high arterial blood pressure, has been associated with an increased risk of coronary heart disease in middle-aged subjects but also to a reduction in pulmonary function [29]. In this regard, Leone *et al.* reported that lung function impairment was associated with metabolic syndrome independently of age, sex, smoking status, alcohol consumption, educational level, body mass index, leisure-time physical activity and cardiovascular disease history [29]. Following factor analysis, three main elements were inversely related to lung function: low high-density lipoprotein cholesterol/high triglycerides, high fasting glycemia/high blood pressure and abdominal obesity, although this last factor was the strongest predictor of lung function impairment, for both women and men.

In conclusion, these results suggest that obesity is associated with variations in pulmonary function and increases in systemic inflammation although the obesity-related changes in lung function do not seem to be significantly related to systemic inflammation.

List of Abbreviations

AT	Adipose Tissue
BMI	Body Mass Index
CRP	C-reactive protein
CT	Computed Tomography
ELISA	Enzyme-Linked Immunosorbent Assay
ERV	Expiratory Reserve Volume
IL-6	Interleukine-6
FRC	Functional Residual Capacity
Hs-CRP	High-sensitive C-reactive protein
MS	metabolic syndrome
No-MS	No metabolic syndrome
RV	Residual Volume
TNF-α	Tumor Necrosis Factor Alpha
VC	Vital Capacity
WBC	White blood cell counts
WC	Waist Circumference

References

1. Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. *Can Respir J* 2006;13:203-10.
2. Lazarus R, Sparrow D, Weiss ST. Effects of obesity and fat distribution on ventilatory function: the normative aging study. *Chest* 1997;111:891-8.
3. Ochs-Balcom HM, Grant BJ, Muti P, Sempos CT, Freudenheim JL, Trevisan M, Cassano PA, Iacoviello L, Schünemann HJ. Pulmonary function and abdominal adiposity in the general population. *Chest* 2006;129:853-62.
4. Despres JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 2001;322:716-20.
5. Staiger H, Tschritter O, Machann J, Thamer C, Fritsche A, Maerker E, Schick F, Häring HU, Stumvoll M. Relationship of serum adiponectin and leptin concentrations with body fat distribution in humans. *Obes Res* 2003;11:368-72.
6. Fantuzzi G. Adiponectin and inflammation: consensus and controversy. *J Allergy Clin Immunol* 2008;121:236-30.
7. Ford ES. The metabolic syndrome and C_reactive protein, fibrinogen, and leukocyte count: findings from the Third Nationa Health and Nutrition Examination Survey. *Atherosclerosis* 2003; 168: 351-58.
8. Das UN. Obesity, metabolic syndrome X, and inflammation. *Nutrition* 2002; 18: 430-2.
9. Luc G, Bard J-M, Juhan-Vague I, Ferrieres J, Evans A, Amouyel P, Arveiler D, Fruchart J-C, Ducimetiere P. C-reative protein, interleukine-6, and fibrinogen as predictors of coronary heart disease: the PRIME study. *Arterioscler Thromb Vasc Biol* 2003; 23: 1255-61.
10. Sood A, Ford ES, Camargo CA, Jr. Association between leptin and asthma in adults. *Thorax* 2006;61(4):300-5.
11. Sood A, Cui X, Qualls C, Beckett WS, Gross MD, Steffes MW, Smith LJ, Jacobs DR Jr. Association between asthma and serum adiponectin concentration in women. *Thorax* 2008;63:877-82.
12. Ferland M, Després JP, Tremblay A, Pinault S, Nadeau A, Moorjani S, Lupien PJ, Thériault G, Bouchard C. Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. *Br J Nutr* 1989;61:139-48.
13. Meneely GR, Kaltreider NL. The volume of the lung determined by helium dilution. Description of the method and comparison with other procedures. *J Clin Invest* 1949;28:129-39.
14. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS workshop on lung volume measurements. Official statement of the European Respiratory Society. *Eur Respir J* 1995;8:492-506.
15. Ledue TB, Weiner DL, Sipe JD, Poulin SE, Collins MF, Rifai N. Analytical evaluation of particle-enhanced immunonephelometric assays for C-reactive protein, serum amyloid A and mannose-binding protein in human serum. Ann Clin Biochem. 1998;35:745-53.
16. Alberti KG.,Zimmet P, Shaw J. IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; 366: 1059-62.
17. Babb TG, Wyrick BL, DeLorey DS, Chase PJ, Feng MY. Fat distribution and end-expiratory lung volume in lean and obese men and women. *Chest* 2008;134:704-11.
18. Ray CS, Sue DY, Bray G, Hansen JE, Wasserman K. Effects of obesity on respiratory function. *Am Rev Respir Dis* 1983;128:501-6.
19. Biring MS, Lewis MI, Liu JT, Mohsenifar Z. Pulmonary physiologic changes of morbid obesity. *Am J Med Sci* 199;318:293-7.
20. Chlif M, Keochkerian D, Feki Y, Vaidie A, Choquet D, Ahmaidi S. Inspiratory muscle activity during incremental exercise in obese men. *Int J Obes (Lond)* 2007;31:1456-63.
21. Boulet LP, Turcotte H, Boulet G, Simard B, Robichaud P. Deep inspiration avoidance and airway response to methacholine: Influence of body mass index. *Can Respir J* 2005;12:371-6.
22. 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;178:469-75.
23. Watz H, Waschki B, Kirsten A, Müller K-C, Kretschmar G, Meyer T, Holz O, Magnussen H. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009; 136: 1039-46.
24. Aronson D, Roterman I, Yigla M, Kamer A, Avizohar O, Sella R, Bartha P, Levy Y, Markiewicz W. Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. *Am J Respir Crit Care Med* 2006; 174: 626-32.
25. Kony S, Zureik M, DrissF, Neukirch C Leynaert B, Neukirch F. Association of bronchial responsiveness and lung function with C-reactive protein (CRP): a population based study. *Thorax* 2004; 59: 892-6.
26. Rasmussen F, Mikkelsen D, Hancox RJ, Lambrechtsen J, Nybo M, Hansen HS, Siersted HC. High-sensitive C-reactive protein is associated with reduced lung function in young adults. *Eur Respir J* 2009; 33: 382-8.
27. Hancox RJ, Poulton R, Greene JM, Filsell S, McLachlan CR, Rasmussen F, Taylor DR, Williams MJ, Williamson A, Sears MR. Systemic inflammation and lung function in young adults. Thorax 2007; 62: 1064-8.
28. Fogarty AW, Jones S, Britton JR, Lewis SA, McKeeveer TM. Systemic inflammation and decline in lung function in a general population: a prospective study. *Thorax* 2007; 62: 515-20.
29. Leone N, Courbon D, Thomas F, Bean K, Jégo B, Leynaert B, Guize L, Zureik M. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med*. 2009;179:509-16