# Pulmonary Function Changes in the Older adults with and without Metabolic Syndrome

**Maysa Brandao Rangel** ( maysarangel_4@hotmail.com )
Federal University of Sao Paulo
**Renilson Moraes-Ferreira**
Federal University of Sao Paulo
**Manoel Oliveira-Junior**
Brazilian Institute of Teaching and Research in Pulmonary and Exercise Immunology (IBEPIPE)
**Alana Santos-Dias**
Brazilian Institute of Teaching and Research in Pulmonary and Exercise Immunology (IBEPIPE)
**André Bachi**
Federal University of Sao Paulo
**Giovana Gabriela-Pereira**
Brazilian Institute of Teaching and Research in Pulmonary and Exercise Immunology (IBEPIPE)
**Simone de Oliveira Freitas**
Brazilian Institute of Teaching and Research in Pulmonary and Exercise Immunology (IBEPIPE)
**Amanda Araújo-Rosa**
Brazilian Institute of Teaching and Research in Pulmonary and Exercise Immunology (IBEPIPE)
**Luis Oliveira**
Post-graduation Program in Human Movement and Rehabilitation, UniEvangélica
**Claudio Frison**
Brazilian Institute of Teaching and Research in Pulmonary and Exercise Immunology (IBEPIPE)
**Raghavan Raju**
Augusta University
**P Balagopal**
Mayo Clinic
**Rodolfo Vieira**
Federal University of Sao Paulo

---

**Research Article**

**Keywords:** aging, metabolic syndrome, lung function, lung mechanics, lung inflammation, pulmonary immunology

**Posted Date:** March 5th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-271946/v1

# Abstract

Low-grade inflammation associated with metabolic syndrome (MS) triggers alterations in several organs, but its effects on pulmonary functional and immunological response in older adults are unknown. This cross-sectional study investigated such responses in older adults with and without MS. The study consisted of 77 older adults with MS (68 ± 3 years old) and without MS (67 ± 3 years old). Impulse oscillometry (IOS) was used to evaluate airway and tissue resistance and reactance. Biomarkers of systemic and pulmonary inflammation and fibrosis were studied. Total resistance of respiratory system (R5Hz; $p < 0.009$), and resistance of proximal (R20Hz; $p < 0.001$) and distal (R5Hz-R20Hz; $p < 0.004$) airways were impaired in MS individuals compared to those without MS. The levels of pro-inflammatory (leptin; IL-1beta; IL-8, $p < 0.001$; TNF-alpha, $p < 0.04$) and pro-fibrotic (VEGF, $p < 0.001$) factor increased in MS, while reduced levels of anti-inflammatory cytokines (adiponectin; IL-1ra; IL-10; $p < 0.001$), and anti-fibrotic (relaxin 1; relaxin 3; Klotho, $p < 0.001$) factors were found. We conclude that MS accelerates lung function and mechanics impairment in older adults in detriment of an imbalance between pro and anti-inflammatory and fibrotic mediators. Furthermore, this study shows that the lungs also are a target organ in MS, deserving clinical assessment in older adults' population.


# 1. Introduction

Metabolic syndrome (MS) is characterized by the coexistence of at least three of the following clinical features: abdominal obesity (AO), hyperglycemia, hypertriglyceridemia, hypertension and low levels of high-density lipoprotein (HDL) (Alberti et al.,2009) MS is also associated with low-grade inflammation characterized by increased circulating levels of pro-inflammatory factors, such as interleukin (IL) -1beta, IL-8, tumor necrosis factor alpha (TNF-alpha), leptin, resistin as well as pro-fibrotic growth factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta) (Catrysse,2017). A heightened and chronic state of inflammation in the older adults, known as inflammaging, accelerates the biological aging process and exposes individuals to weakening of the immune responses leading to immunosenescence. In individuals with MS compared to those without MS, inflammaging and immunosenescence are more pronounced and they induce structural and functional alterations in multiple organ systems and thus accelerating the overt manifestation of various diseases such as cardiovascular disease (CVD) and type II diabetes mellitus (T2DM) (Tune et al.,2017). Additionally, the aging process itself entails obligatory changes in various body systems leading to drastic derangements including that in the respiratory system (However, there is a paucity of information on the intrinsic changes in inflammatory status within the respiratory system of the older adults with MS (Skloot, 2017).

Although some controversy exists as to whether MetS is a unique disease entity, its individual components have independently been associated with changes in pulmonary function and or lung diseases in humans (Baffi et al., 2016). The influence of MS on lung mechanics (indicating structural alterations) and pulmonary immune response, however, remains less clear, particularly in the older adults. In fact, chronic respiratory diseases appear to be more frequent in individuals with morbid obesity and

MS vs those without MS (Lee et al.,2019). Previous studies have also reported correlations between systemic inflammation and reduced pulmonary function (Van Huisstede et al.,2013). A recent pre-clinical study showed that obesity induced the development of a specific pro-inflammatory and pro-fibrotic lung phenotype, which might alter lung function (Aquino-Junior et al.,2018), suggesting the potential obesity-related alterations in lung function. In the present study, we tested the hypothesis that in the older adults people with MS the pro-inflammatory and pro-fibrotic response in the respiratory system may enhance the loss of pulmonary function and impaired lung mechanics.

# 2. Methods

### 2.1-Patient Selection

The older adults' women and men for the study were recruited in the Center for Social, Sports and Health Care for Older adults from the municipality of the city of São José dos Campos – SP, Brazil. World Health Organization (WHO) criteria for older adults' people defined as 60 years of age or older (OMS,2005) was used for recruitment. For inclusion in the study the participants should be able to perform spirometry evaluation (forced maneuver). Exclusion criteria included, (i) history of smoking, (ii) diagnosis of respiratory disease, (iii) chronic degenerative, autoimmune, or neurological diseases, (iv) regular physical activity.

From a total 807 potential participants screened for the study, 77 (68± 3 years old; 26 men, 51 women) with MS and 77 (67±3 years old; 21 men, 56 women) without MS eligible participants were randomly selected and enrolled in the study. The diagnosis of MS was according to the American Heart Associantion.[1] Briefly, individuals presenting at least three of the following characteristics were classified as with MS: abdominal obesity (Obesity: BMI >26 or waist-to-hip ratio >0.9 (male) or >0.85 (female); hyperglycemia (hyperinsulinaemia: top 25% of fasting insulin values from non-diabetic population), hypertriglyceridemia (triglycerides ≥1.7 mmol/L or HDL cholesterol <0.9 (male) or <1.0 (female) mmol/L), hypertension (blood pressure >140/90 mm Hg) and low levels of high-density lipoprotein (Low HDL cholesterol: <1.0 mmol/L (male), <1.3 mmol/L (female) (Alberti et al.,2009).

The present study and all procedures performed were approved by the ethics committee of the University of São Paulo (53344616.6.0000.5511) and appropriate consents were obtained from the participants included in the study. The study protocol was in accordance to institutional guidelines and the Declaration of Helsinki. Informed consent was obtained from all the participants prior to the study.

*The authors confirm that the data supporting the findings of this study are available within the article.*

### 2.2-Clinical, Biochemical and Anthropometric Evaluation

All volunteers were systematically evaluated and followed by a geriatrician from the Older adults Houses of municipality of São José dos Campos city. The age (years), body mass (Kg), height (m), body mass index (BMI), and waist circumference (cm), were measured as part of the clinical evaluation of the

volunteers. The venous blood (5 mL) was collected from each subject using vacuum tubes and 25µl of the total blood was immediately used for the whole blood hematology analysis. The remaining blood was centrifuged at 900g, 4ºC, for 7 minutes and the serum was stored at -86ºC until analysis. Biochemical measurements consisted of total cholesterol (REF76), HDL cholesterol (REF13) and triglycerides (REF87) in the sera by using commercial colorimetric kits from Labtest® (Lagoa Santa, MG, Brazil). The whole blood analysis (white and red cells) was performed using the automated hematology analyzer (Roche, Sysmex XS-800i, Europe GmbH, Germany). Table 1 summarizes the clinical, biochemical and anthropometric characteristics of the volunteers. The serum was used for the quantification of inflammatory and fibrotic mediators by *enzyme-linked immunosorbent assay (ELISA), by using SpectraMax i3 (Molecular Devices®, USA).*

### 2.3-Breath Condensate Collection and Analysis

The exhaled breath condensate (BC) was collected using the RT-Tube (Respiratory Research, USA) according to the manufacturer's instructions. In brief, approximately 1-2 ml of BC was collected from each volunteer in 10-15 minutes and the samples were stored at -86ºC until analysis. The BC was used for the quantification of inflammatory and fibrotic mediators by *enzyme-linked immunosorbent assay (ELISA), using SpectraMax i3 (Molecular Devices®, USA).*

### 2.4-Measurement of Inflammatory and Fibrotic Mediators in Serum and in Breath Condensate

Pro-inflammatory cytokines [(IL-1beta, Biolegend 437006); (IL-8, R&D Systems DY208), (TNF-alpha, R&D Systems DY210), anti-inflammatory cytokines (IL-1ra, R&D Systems DY280) (IL-10, Biolegend 430603), pro-fibrotic (VEGF, R&D Systems DY293) and anti-fibrotic factors (relaxin 1, R&D Systems DY3257), (relaxin 3, R&D Systems DY3107), and (Klotho, R&D Systems DY5334)] were evaluated by using ELISA DuoSet kits (R&D Systems®, USA) or ELISA Max (Biolegend®, USA), according to manufacturer's instructions. The readings were performed using the multi-reader platform SpectraMax i3 (Molecular Devices®, USA).

### 2.5-Measurement of Pulmonary Function and Mechanics

The lung function and mechanics were evaluated by using spirometry coupled to impulse oscillometer (Masterscreen Impulse Oscillometry – MS-IOS; Jaeger®, Germany) using the American Thoracic Society (ATS) criteria (Culver et al.,2017).The spirometric variables measured were: Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), the FEV1/FVC ratio, and the forced expiratory flow 25-75% (FEF25-75%)] using the reference values previously established for Brazilian population (Pereira et al.,2007). The lung mechanics were evaluated by impulse oscillometry (IOS), for the following parameters: R5Hz (total respiratory system resistance), R20Hz (resistance of proximal airways), R5Hz-R20Hz (resistance of distal airways), X5Hz (tissue reactance), RCentral (resistance of proximal tissue), and RPeripheral (resistance of distal tissue) (Pereira et al.,2007).

### 2.6-Measurement of General and Respiratory Muscle Strength

Hand grip strength, which represented the overall muscle strength was evaluated by using a hand grip dynamometer (Jamar®, Sammons Preston Rolyan, Boilingbrook, IL, USA) (Fuller et al.,2018). The results were presented in kilogram (Kg). The respiratory muscle strength was evaluated by using a manovacuometer (MVD-300 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil) by measuring the maximal inspiratory (MIP) and expiratory (MEP) pressure. The results were presented in $cmH_2O$ (Cavalheri et al.,2019).

# 3. Statistical Analysis

Data of clinical characteristics were summarized by individuals with MS and without MS. The quantitative variables were summarized by mean (SD) or median (interquartile interval [IQR], when appropriate). The normality of the data was analyzed by Shapiro-Wilk test and the correlation by Pearson test. Non-paired t-test was used to calculate significance and, p value of $<0.05$ was considered significant. Categorical variables were summarized by numbers and percentages. A Pearson correlation was performed to examine the association of cytokines with pulmonary function. The GraphPad Prism 5.0 was used to perform the statistical analysis and build the graphs.

# 4. Results

The study included equal number (n=77 each) of subjects with MS and without MS. The clinical, biochemical and anthropometric characteristics of the subjects are shown in Table 1. Both groups were similar in age, height, total leukocytes, eosinophils and lymphocytes. However, the older adults with MS had significantly increased mean body weight, body mass index (BMI), systolic and diastolic blood pressure, waist circumference, total cholesterol, HDL cholesterol, triglycerides, basophils, monocytes and neutrophils when compared to NMS.

### 4.1-Table

**Table 1-** Clinical and anthropometric characteristics of older adults patients with (n = 77) and without (n = 77) MS.

| PARAMETERS | M.S | N.M.S | P value |
|---|---|---|---|
| Age (years) | 67.44 (±3,5) | 68.52 (±3,1) | 0.2737 |
| Men | 41 | 40 | |
| Women | 36 | 37 | |
| Weight (kg) | 74.03 (±4,2) | 65.89 (±6,3) | 0.0002 |
| Height (m) | 1,58 (±4,2) | 1,58 (±4,6) | 0.5086 |
| BMI (kg/m$^2$) | 30.43 (±2,3) | 25.88 (±3,5) | 0.0002 |
| Systolic blood pressure (mmHg) | 142,1(±1,4) | 118,1(±1,4) | 0.0002 |
| Diastolic blood pressure (mmHg) | 95,4 (±0,7) | 74,4 (±0,9) | 0.0002 |
| Waist circumference (cm) | 92.24 (±4,7) | 78.85 (±1,6) | 0.0004 |
| Total cholesterol (mg/dl) | 197.04 (±17,7) | 123.67 (±10,2) | 0.0082 |
| HDL cholesterol (mg/dl) | 39.09 (±7,7) | 45.22 (±7,9) | 0.0002 |
| Triglycerides (mg/dl) | 242.62(±6,2) | 133.59 (±7,0) | 0.0002 |
| Total leukocytes (cells/mm$^3$) | 5.96 (±2,0) | 6.22 (±2,7) | 0.5940 |
| Basophils (cells/mm$^3$) | 24.5 (±7,0) | 26.8 (±8,7) | 0.0089 |
| Monocytes (cells/mm$^3$) | 434.5 (±4,1) | 318.42 (±3,2) | 0.0026 |
| Eosinophils (cells/mm$^3$) | 188.22 (±2,6) | 186.42 (±2,8) | 0.7044 |
| Lymphocytes (cells/mm$^3$) | 2.5 (±2,4) | 2.46 (±2,8) | 0.2544 |
| Neutrophils (cells/mm$^3$) | 3.25 (±2,3) | 2.52 (±2,3) | 0.0029 |

### 4.2-Systemic Inflammatory and Fibrotic Factors

Figure 1 shows the levels of circulating adiponectin, adiponectin/leptin ratio, and pro-fibrotic (VEGF), and anti-fibrotic (Klotho, Relaxin-1, Relaxin-3) factors in the serum. The results demonstrate increased the levels of pro-inflammatory mediators in the participants with MS [(IL-1beta, <0.0001); (IL-8, p<0.0001); (TNF-alpha, p<0.0001); (leptin, p<0.0001) and pro-fibrotic (VEGF p<0.0001)] compared to without MS. There was a significant decrease in the levels of anti-inflammatory factors [(IL-1ra, p<0.04); (IL -10, p<0.0001); (adiponectin, p<0.0001); (adiponectin/leptin ratio, p<0.0001) and anti-fibrotic (Klotho, p<0.0001; relaxin-1, p<0.0001; relaxin-3, p<0.0001)] in the older adults with MS compared to without MS.

### 4.3-Pulmonary Inflammatory and Fibrotic Factors

Figure 2 shows the levels of pro-inflammatory (IL-1beta, Figure 2A; IL-8, Figure 2B; TNF-alpha, Figure 2C; leptin, Figure 2F), anti-inflammatory (IL-1ra, Figure 2D; IL-10, Figure 2E; adiponectin, Figure 2H; adiponectin/leptin ratio, Figure 2G), pro-fibrotic (VEGF, Figure 2I), anti-fibrotic (Klotho, Figure 2J; relaxin-1, Figure 2K; relaxin-3, Figure 2L) in breath condensate. The results demonstrated increased levels of pro-inflammatory factors [(leptin $p<0.04$; IL-1beta $p<0.04$; IL-8 $<0.0001$; TNF-alpha $p<0.04$) and pro-fibrotic (VEGF $p<0.0001$)] in breath condensate in the participants with MS compared to without MS. However, decreased the levels of anti-inflammatory factors [(adiponectin, $p<0.0001$; IL-1ra $p<0.0001$; IL-10 $p<0.0001$; adiponectin/leptin ratio $p<0.0001$) and anti-fibrotic (relaxin 1 $p<0.0001$; relaxin 3 $p<0.0001$; Klotho $p<0.0001$)] in breath condensate were observed in those with MS compared to without MS.

### 4.4-Lung Function with Metabolic Syndrome

Figure 3 shows the lung function parameters, FVC, (Figure 3A); FEV-1, (Figure 3B); FEV1/FVC, (Figure 3C); Peak Expiratory Flow, Figure 3D; Maximum Expiratory Flow 25%, Figure 3E; Maximum Expiratory Flow 50%, Figure 3F; Maximum Expiratory Flow 75%, Figure 3G) in MS and without MS groups. The results demonstrated reduced FEV1 ($p<0.0007$); PEF ($p<0.0003$); MEF25 $p<0.003$; MEF75 $p<0.0001$) in those with MS, compared to without MS. In addition, as shown in Figure 5, a positive correlation was found, between MEF25-75 with the levels of pulmonary (breath condensate) VEGF ($R=0.2770$; $p<0.0468$), and pulmonary (breath condensate) leptin; $R=0.2803$; $p<0.0463$) as well as FEV1/FVC with the levels of pulmonary (breath condensate) relaxin 1 (; $R=0.3113$; $p<0.0448$) (Figure 5).

### 4.5-Lung Mechanics in Metabolic Syndrome

Figure 4 shows the lung mechanics parameters such as R5Hz, R20Hz, R5Hz-R20Hz, X5Hz, RCentral, and RPeripheral. The results demonstrated increased resistance of respiratory system (R5Hz; $p<0.0091$), proximal airways (R20Hz; $p<0.0011$), distal airways (R5Hz-R20Hz; $p<0.04$), tissue reactance (X5Hz $p<0.0020$), resistance of proximal tissue (RCentral $p<0.0001$) and resistance of distal tissue (RPeripheral $p<0.0188$) in MS compared to without MS. In addition, as demonstrated in Figure 5, a positive correlation was found between central tissue resistance (RCentral) and the levels of pulmonary (breath condensate) IL-1beta ($R=0.1340$; $p<0.0333$) (Figure 5).

### 4.6-Respiratory Muscle Strength and Hand Grip Strength

Figure 6 shows the general strength evaluated by hand grip [Figure 6A (right hand) and 6B (left hand)] and the respiratory muscle strength, evaluated by maximal inspiratory pressure (MIP) (Figure 6C) and maximal expiratory pressure (MEP) (Figure 6D). The results demonstrated that MS did not induce changes in general strength [(Figure 6A, right hand, $p>0.05$) and (Figure 6B, left hand, $p<0.0009$) compared with without MS group. However, respiratory muscle strength (MIP, $p<0.0009$) and (MEP, $p<0.0096$) in the MS group were lower compared with without MS group.

## 5. Discussion

The simultaneous measurement of various parameters related to lung function and structure, pro- and anti-inflammatory factors and fibrotic factors in the present study showed that the systemic immune response in the older adults participants with MS was associated with the worsening of lung function. Both pulmonary and systemic inflammatory and fibrotic factors showed alterations in those with MS compared to their without counterparts. While the hand grip, a measure of general strength was preserved in both MS and without MS, there was a significant deterioration in respiratory muscle strength in the older adults with MS. The functional and structural alterations observed in the lungs (airways and parenchyma), in the older adults with MS suggest that the role of lungs as a potential target organ in the older adults in the setting of MS. The increases in airway and tissue resistance in the lungs, suggesting the process of remodeling, is characterized by the accumulation of extracellular matrix proteins (collagen, elastin, proteoglycans, laminins) and reflect the structural and functional alterations in the lungs (Aquino-Junior et al.,2018) The alterations of the inflammatory milieu in the lungs is considered a causative factor in its remodeling process (Aquino-Junior et al., 2018, Mirhafez et al.,2015)

Metabolic syndrome leads to immune hyperactivation mainly characterized by increased levels of pro-inflammatory cytokines (i.e. IL-1beta, IL-6, IL-8, TNF-alpha, etc), pro-inflammatory adipokine (leptin) and pro-fibrotic growth factors (i.e. VEGF, TGF-beta, etc) (Aquino-Junior et al., 2018, Mirhafez et al.,2015). The increased levels of proinflammatory mediators can disrupt the release of anti-inflammatory cytokines such as IL-1ra, IL-10, and anti-inflammatory adipokines such as adiponectin, accounting for impairment of the normal immune function, alter normal lung function and may perpetuate the development and progression of chronic diseases (Aquino-Junior et al.,2018, Andersen et al.,2016). Previous reports have showed robust correlations of MS with structural and functional alterations in the heart (Sherling et al.,2017), blood vessels (Sherling et al.,2017) and kidneys (Sherling et al.,2017). The present study showed that concomitant with the systemic responses, there were strong pro-inflammatory and pro-fibrotic responses in the lungs in the participants with MS. We also observed a reduction in anti-inflammatory response in the lungs of older adults with MS.

Metabolic alterations and impairments are classic features of aging, and they are typically mediated by a compromised immune response leading to inflammaging and *immunosenescence (Wong et al.,2019, Salminen 2020)* Although inflammaging and immunosenescence are well characterized in humans, the contribution of MS towards its development and/or progression is less understood (*Wong et al.,2019; Salminen 2020)*. The present study highlights that MS in the older adults is associated with substantially increased release of systemic pro-inflammatory mediators such as IL-1beta, IL-8, TNF-alpha, leptin, and the pro-fibrotic mediator, VEGF, when compared to older adults with without MS. More importantly, the study also showed for the first time that anti-inflammatory mediators such as IL-1ra, IL-10, and adiponectin, and anti-fibrotic mediators such as Klotho, Relaxin 1, Relaxin 3 (Buendia-Roldan et al.,2019, Samuel et al.,2017) are reduced in the older adults with MS. Such effects observed in the older adults with MS may accelerate the process of senescence increasing the risk for CVD (Andersen et al., 2016, Guarner and Rubio,2015). A previous study demonstrated that in patients with idiopathic interstitial lung diseases, reduced serum levels of klotho were associated with reduced lung function (Buendia-Roldan et

al.,2019). This is similar to the data in the present study with reduced levels of klotho in serum related to impaired lung function in the older adults with MS.

Further, in the current study, there was a positive correlation between impaired pulmonary immune response (increased levels of pro-inflammatory and pro-fibrotic and reduction of anti-inflammatory and antifibrotic mediators) and impaired pulmonary and mechanical function. The presentation of an amplified inflammatory state in the lungs and systemically, in the older adults with MS is interesting, particularly considering the lack of data in this population. While the underlying mechanisms remain unclear, the present study showed that such pro-inflammatory and pro-fibrotic responses in the lungs were associated with increased resistance of the respiratory system (R5Hz), proximal airways (R20Hz), distal airway (R5Hz-R20Hz) and proximal (RCentral) and distal (RPeripheral) pulmonary tissue, in addition to increases in the deepest resistance of the distal airways (X5Hz). In fact, the impairment of pulmonary mechanics observed in the present study (as described above) reflects structural changes in different pulmonary compartments (Brashier,2015), similar to the detrimental changes that chronic subclinical inflammation and pro-fibrotic mediators provoke in the cardiovascular system, both structure and function (Bartekova et al.,2018).

Increased levels of VEGF have been associated with different pulmonary diseases, such as asthma, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis, with altered established fibrotic processes (Lee et al., 2004, Westergren-Thorsson et al.,2018, Barrat et al.,2018). VEGF induces fibrosis via fibroblast and smooth muscle proliferation and activation, leading to synthesis and release of larger amounts of extracellular matrix proteins, such as collagen and elastic fibers, proteoglycans and laminins. (Lee et al., 2004, Westergren-Thorsson et al.,2018, Barrat et al.,2018). The present study revealed that older adults with MS presents higher levels of VEGF compared with NMS, in circulation (systemic response) as well as in the breath condensate (pulmonary response). Thus, the airway obstruction found in older adults with MS could be the result of central airway remodeling due to pro-inflammatory and pro-fibrotic pulmonary processes (Arimura et al.,2012, Park et al.,2018). For the distal airways, it can be due to a decrease in the retraction capacity of the lung tissue, induced by accumulation of elastic fibers that may result in increased lung elastance, as observed in the present study through the increases in RPeripheral values (Fehrenbach et al.,2017).

Beyond the impairment of lung function and mechanics, and of systemic and pulmonary immune response, the present study also showed a reduction in the respiratory muscle strength, while the general muscle strength remained stable, in older adults with MS compared to without MS. This is a clinically significant finding with respect to the impairment of lung function and mechanics, since the number of cardiorespiratory events in older adults is typically higher than in younger population. These are even at higher magnitude in the older adults with MS (Rodgers et al.,2019). Likewise, during the cardiorespiratory events, the need for intubation following mechanical ventilation is higher among the older adults and the impaired lung function and reduced diaphragm muscle mass may adversely affect the prognosis (Who et al.,2019). Thus, the reduced respiratory muscle strength in older adults with MS observed in this study

should be carefully considered in critically ill older adults, as these patients are more susceptible and may stay longer under mechanical ventilation.

The present study has a few limitations worth noting. The blood glucose levels were not measured, since all MS older adults were diagnosed with diabetes, but well-controlled and stable under standard medication provided by the Brazilian government for at least 24 months. The lack of computerized tomography (CT) measurement of structural changes in the lungs is also a limitation and the related data should be considered with caution. Further, we did not determine the impact of each component of the MS separately in the derangement of lung structure and function.

In conclusion, MS affects lung mechanics, function, and immunological response in the older adults individuals. Given the wide prevalence of MS in the general older adults population, it is crucial that we continue to further understand the underlying mechanisms of how the metabolic derangements in the older adults impact the lung and how to prevent complications. In fact, the present study highlights the clinical relevance of assessing not only systemic inflammation but also pulmonary inflammation along with lung mechanics in the older adults with MS. Such an approach will enable the development of more directed therapeutic interventions to improve the outcomes in older adults people with MS. Future research should also address if optimally controlling the components of MS early in its clinical course will have a protective effect and/or contribute to the amelioration of the path towards inflammaging and/or immunosenescence of the lungs via attenuation of the inflammatory pathways, both systemically and in the respiratory system.

# Declarations


### Acknowledgements

This study was supported by Sao Paulo Research Foundation (FAPESP), grants #2012/15165-2. MARBR holds a PhD fellowship from FAPESP #2019/05739-0. RMF holds a PhD fellowship from FAPESP #2019/11008-9. Conselho Nacional de Pesquisa e Desenvolvimento (CNPq), grants 427889/2016-2 and 313299/2018-8.


### Conflict of Interest

All authors state no conflict of interest related to this publication.

# References


1. Alberti KG et. al.; International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart

Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120:1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644.

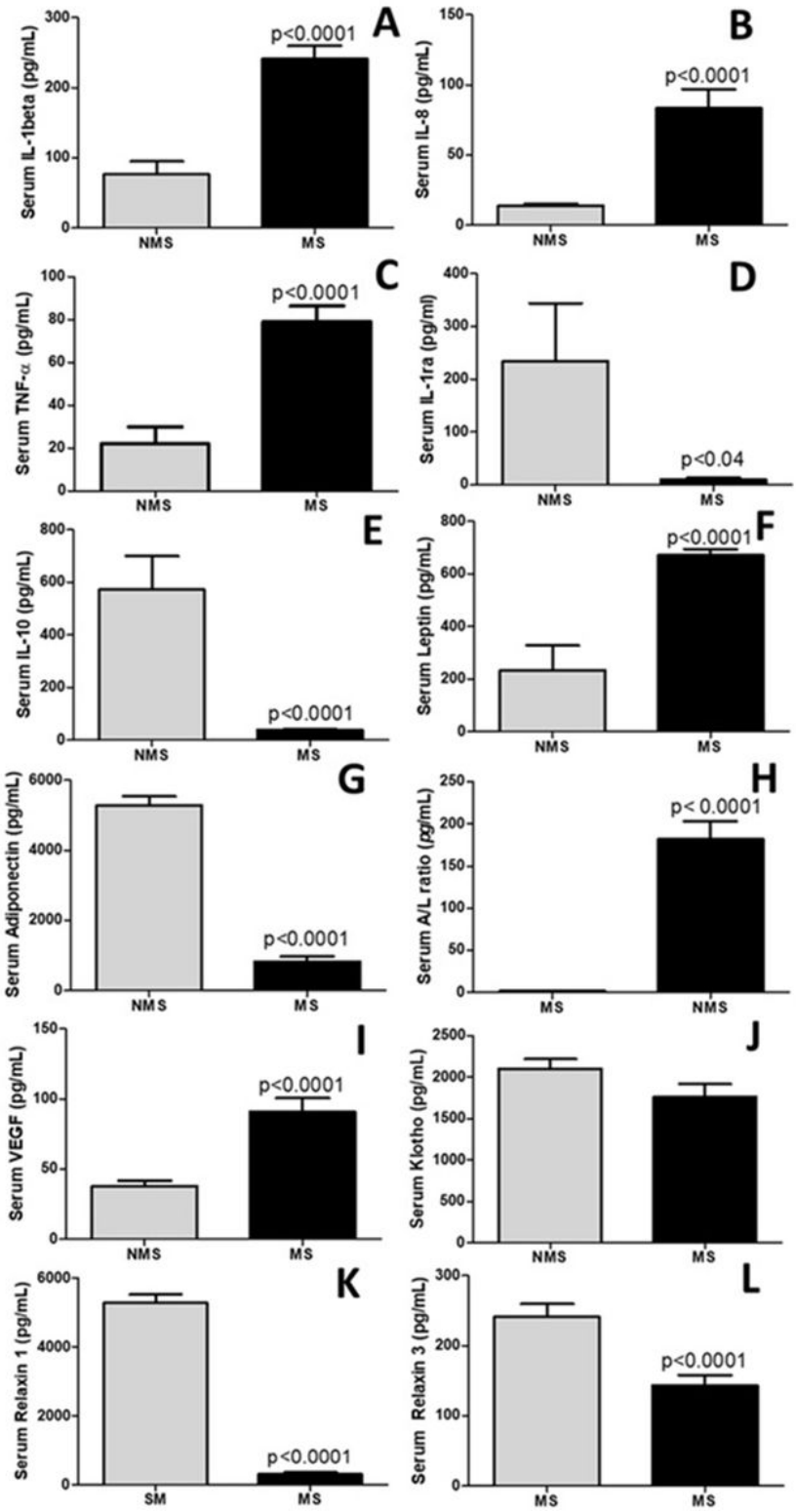
2. Andersen CJ, Murphy KE, Fernandez ML. Impact of Obesity and Metabolic Syndrome on Immunity. Adv Nutr. 2016 Jan 15;7(1):66-75. doi: 10.3945/an.115.010207.
3. Aquino-Junior JCJ et. al. Aerobic exercise inhibits obesity-induced respiratory phenotype. Cytokine. 2018 Apr; 104:46-52. doi: 10.1016/j.cyto.2017.12.025. Epub 2018 Feb 15. PMID: 29454302.
4. Arimura K, Aoshiba K, Tsuji T, Tamaoki J. Chronic low-grade systemic inflammation causes DNA damage in the lungs of mice. Lung. 2012 Dec;190(6):613-20. doi: 10.1007/s00408-012-9414-8. Epub 2012 Sep 11. PMID: 22965854.
5. Baffi CW, et. al. Metabolic Syndrome and the Lung. Chest. 2016 Jun;149(6):1525-34. doi: 10.1016/j.chest.2015.12.034. Epub 2016 Jan 20. PMID: 26836925; PMCID: PMC4944780.
6. Barratt SL, Flower VA, Pauling JD, Millar AB. VEGF (Vascular Endothelial Growth Factor) and Fibrotic Lung Disease. Int J Mol Sci. 2018 Apr 24;19(5):1269. doi: 10.3390/ijms19051269. PMID: 29695053; PMCID: PMC5983653
7. Bartekova M, Radosinska J, Jelemensky M, Dhalla NS. Role of cytokines and inflammation in heart function during health and disease. Heart Fail Rev. 2018 Sep;23(5):733-758. doi: 10.1007/s10741-018-9716-x. PMID: 29862462.
8. Brashier B, Salvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulse oscillometry system. Breathe (Sheff). 2015 Mar;11(1):57-65. doi: 10.1183/20734735.020514. PMID: 26306104; PMCID: PMC4487383.
9. Buendia-Roldan I, Machuca N, Mejía M, Maldonado M, Pardo A, Selman M. Lower levels of α-Klotho in serum are associated with decreased lung function in individuals with interstitial lung abnormalities. Sci Rep. 2019 Jul 25;9(1):10801. doi: 10.1038/s41598-019-47199-0. PMID: 31346213; PMCID: PMC6658567.
10. Catrysse L, van Loo G. Inflammation and the Metabolic Syndrome: The Tissue-Specific Functions of NF-κB. Trends Cell Biol. 2017 Jun;27(6):417-429. doi: 10.1016/j.tcb.2017.01.006. Epub 2017 Feb 23. PMID: 28237661.
11. Cavalheri V, Burtin C, Formico VR, Nonoyama ML, Jenkins S, Spruit MA, Hill K. Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. Cochrane Database Syst Rev. 2019 Jun 17;6(6):CD009955. doi: 10.1002/14651858.CD009955.pub3. PMID: 31204439; PMCID: PMC6571512.
12. Cebron Lipovec N, Beijers RJ, van den Borst B, Doehner W, Lainscak M, Schols AM. The Prevalence of Metabolic Syndrome In Chronic Obstructive Pulmonary Disease: A Systematic Review. COPD. 2016 Jun;13(3):399-406. doi: 10.3109/15412555.2016.1140732. Epub 2016 Feb 25. PMID: 26914392.
13. Culver BH, et. al.; ATS Committee on Proficiency Standards for Pulmonary Function Laboratories. Recommendations for a Standardized Pulmonary Function Report. An Official American Thoracic

Society Technical Statement. Am J Respir Crit Care Med. 2017 Dec 1;196(11):1463-1472. doi: 10.1164/rccm.201710-1981ST. PMID: 29192835.

14. Fehrenbach H, Wagner C, Wegmann M. Airway remodeling in asthma: what really matters. Cell Tissue Res. 2017 Mar;367(3):551-569. doi: 10.1007/s00441-016-2566-8. Epub 2017 Feb 11. PMID: 28190087; PMCID: PMC5320023.
15. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002 Jan 16;287(3):356-9. doi: 10.1001/jama.287.3.356. PMID: 11790215.
16. Fuller LM, El-Ansary D, Button BM, Corbett M, Snell G, Marasco S, Holland AE. Effect of Upper Limb Rehabilitation Compared to No Upper Limb Rehabilitation in Lung Transplant Recipients: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2018 Jul;99(7):1257-1264.e2. doi: 10.1016/j.apmr.2017.09.115. Epub 2017 Oct 16. PMID: 29042172.
17. Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. Interdiscip Top Gerontol. 2015; 40:99-106. doi: 10.1159/000364934. Epub 2014 Oct 13. PMID: 25341516.
18. Lee CG, Link H, Baluk P, Homer RJ, Chapoval S, Bhandari V, Kang MJ, Cohn L, Kim YK, McDonald DM, Elias JA. Vascular endothelial growth factor (VEGF) induces remodeling and enhances TH2-mediated sensitization and inflammation in the lung. Nat Med. 2004 Oct;10(10):1095-103. doi: 10.1038/nm1105. Epub 2004 Sep 19. PMID: 15378055; PMCID: PMC3434232.
19. Mirhafez SR, et.al. Cytokine and growth factor profiling in patients with the metabolic syndrome. Br J Nutr. 2015 Jun 28;113(12):1911-9. doi: 10.1017/S0007114515001038. Epub 2015 May 20. PMID: 25990566.
20. Organização Mundial da Saúde (OMS). *Envelhecimento ativo: uma política de saúde*. World Health Organization. Brasília: Organização Pan-Americana da Saúde (OPAS); 2005. [acessado 2021 fevereiro 9]. Disponível em: http://dtr2001.saude.gov.br/svs/pub/pdfs/envelhecimento_ativo.pdf
21. Park S, Choi NK, Kim S, Lee CH. The relationship between metabolic syndrome and asthma in the older adults. Sci Rep 2018; 8(1): 9378.
22. Pereira Carlos Alberto de Castro, Sato Taeko, Rodrigues Sílvia Carla. Novos valores de referência para espirometria forçada em brasileiros adultos de raça branca. J. bras. pneumol. [Internet]. 2007 Aug [cited 2021 Feb 10];33(4): 397-406.Availablefrom:http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-37132007000400008&lng=en. https://doi.org/10.1590/S1806-37132007000400008.
23. Rodgers JL, et.al. Cardiovascular Risks Associated with Gender and Aging. J Cardiovasc Dev Dis 2019; 6(2): pii: E19. https://doi.org/10.3390/jcdd6020019.
24. Salminen A. Activation of immunosuppressive network in the aging process. Ageing Res Rev. 2020 Jan; 57:100998. doi: 10.1016/j.arr.2019.100998. Epub 2019 Dec 12. PMID: 31838128.
25. Samuel CS, Royce SG, Hewitson TD, Denton KM, Cooney TE, Bennett RG. Anti-fibrotic actions of relaxin. Br J Pharmacol 2017; 174(10): 962–976.

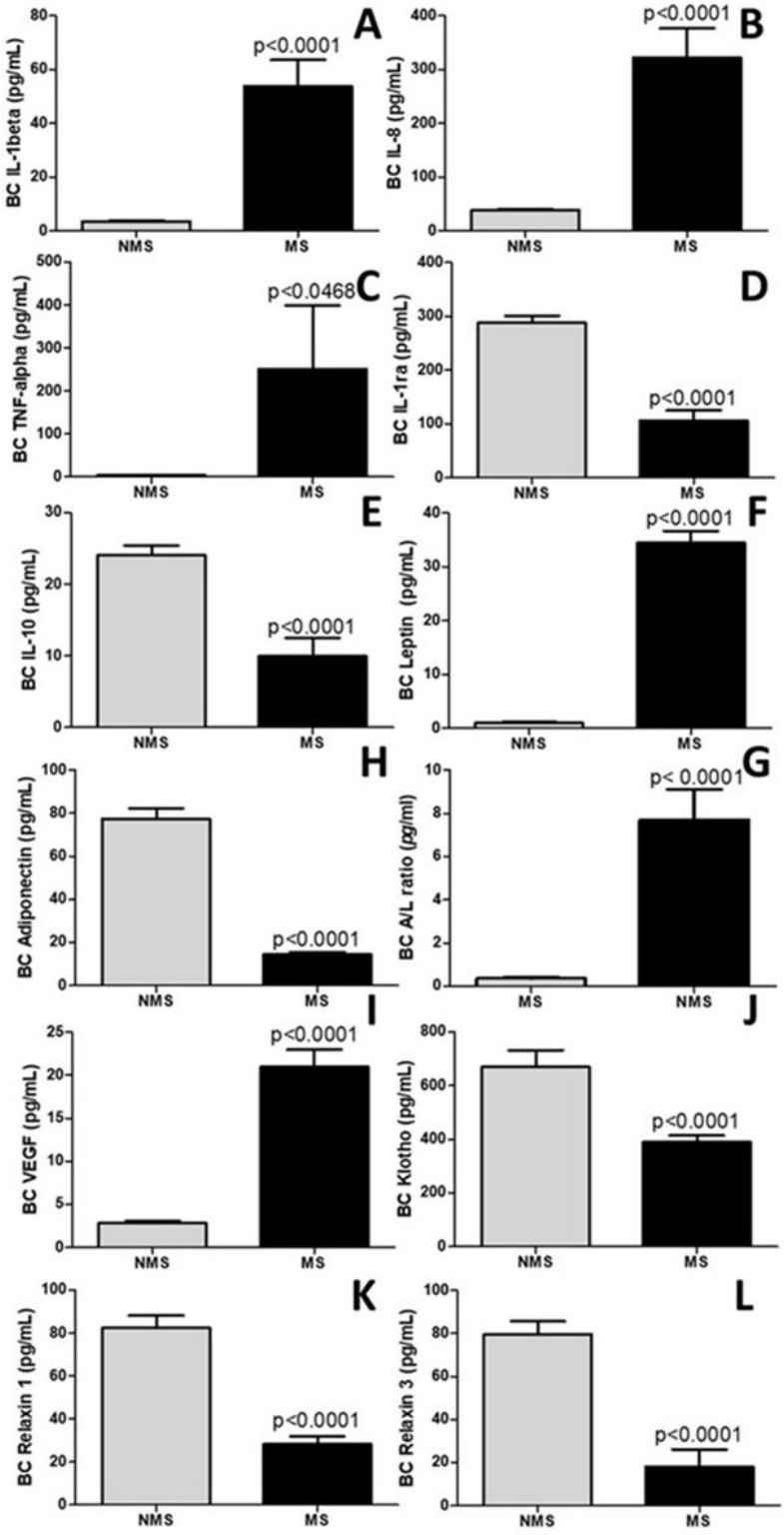
26. Sherling DH, Perumareddi P, Hennekens CH. Metabolic Syndrome. J Cardiovasc Pharmacol Ther 2017; 22(4): 365–367.
27. Skloot GS. The Effects of Aging on Lung Structure and Function. Clin Geriatr Med. 2017 Nov;33(4):447-457. doi: 10.1016/j.cger.2017.06.001. Epub 2017 Aug 19. PMID: 28991643.
28. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. Transl Res. 2017 May;183:57-70. doi: 10.1016/j.trsl.2017.01.001. Epub 2017 Jan 9. PMID: 28130064; PMCID: PMC5393930.
29. Van Huisstede A, et.al. Systemic inflammation and lung function impairment in morbidly obese subjects with the metabolic syndrome. J Obes. 2013; 2013:131349. doi: 10.1155/2013/131349. Epub 2013 Feb 24. PMID: 23509614; PMCID: PMC3595660.
30. Wei X,et.al. Impulse oscillometry system as an alternative diagnostic method for chronic obstructive pulmonary disease. Medicine (Baltimore). 2017 Nov;96(46):e8543. doi: 10.1097/MD.0000000000008543. PMID: 29145259; PMCID: PMC5704804.
31. Westergren-Thorsson G,et.al. VEGF synthesis is induced by prostacyclin and TGF-β in distal lung fibroblasts from COPD patients and control subjects: Implications for pulmonary vascular remodelling. Respirology. 2018 Jan;23(1):68-75. doi: 10.1111/resp.13142. Epub 2017 Aug 22. PMID: 28834088.
32. Wong GCL, et.al. Hallmarks of improved immunological responses in the vaccination of more physically active elderly females. Exerc Immunol Rev. 2019;25:20-33. PMID: 30753128.
33. Woo HY, Oh SY, Lee H, Ryu HG. Evaluation of the association between decreased skeletal muscle mass and extubation failure after long-term mechanical ventilation. Clin Nutr. 2020 Sep;39(9):2764-2770. doi: 10.1016/j.clnu.2019.12.002. Epub 2019 Dec 14. PMID: 31917051.

# Figures



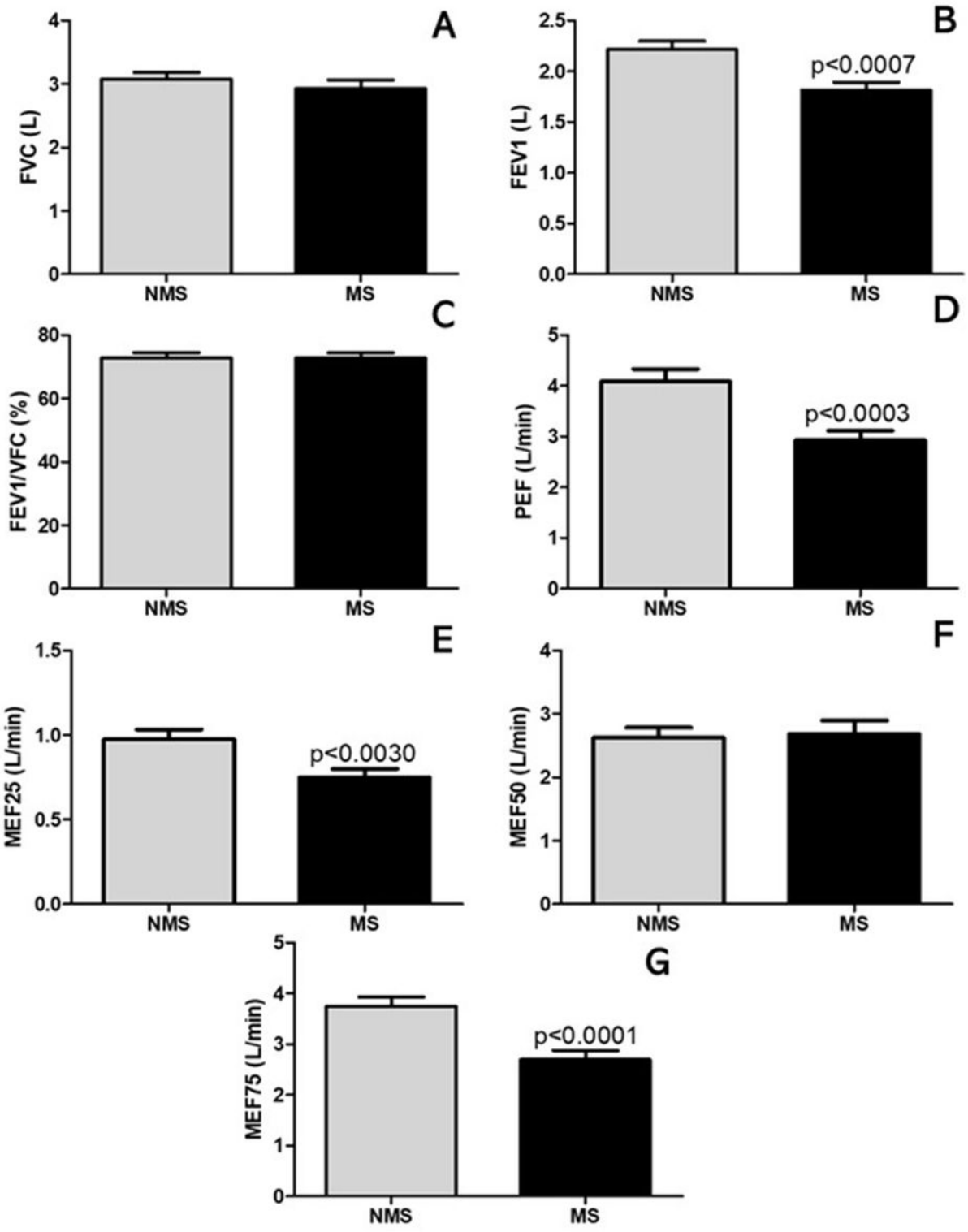

## Figure 1

Immunological mediators in serum from non-metabolic syndrome (NMS) and metabolic syndrome (MS) older adults. Figure 1A (IL1-beta), Figure 1B (IL-08), Figure 1C (TNF-alfa), Figure 1D (IL1ra), Figure 1E (IL-10), Figure 1F (Leptin), Figure 1G (Adiponectin), Figure 1H (Leptin/Adiponectin ratio), Figure 1I (VEGF), Figure 1J (Klotho), Figure 1K (Relaxin 1), Figure 1L (Relaxin 3).



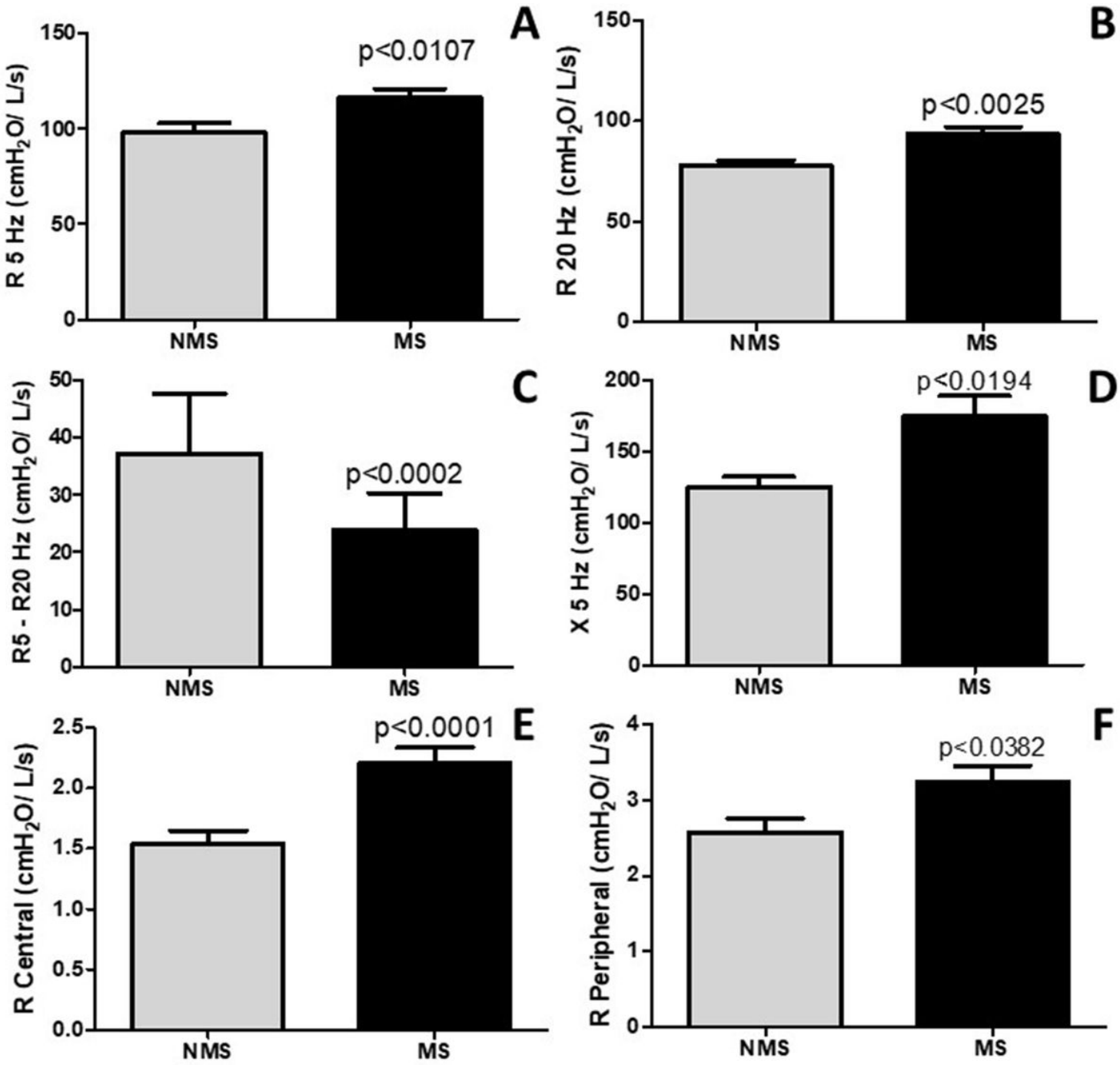

## Figure 2

Immunological mediators in breath condensate from non-metabolic syndrome (NMS) and metabolic syndrome (MS) older adults. Figure 2A (IL1-beta), Figure 2B (IL-08), Figure 2C (TNF-alfa), Figure 2D (IL1ra), Figure 2E (IL-10), Figure 2F (Leptin), Figure 2H (Adiponectin), Figure 2G (Leptin/Adiponectin ratio), Figure 2I (VEGF), Figure 2J (Klotho), Figure 2K (Relaxin 1), Figure 2L (Relaxin 3).



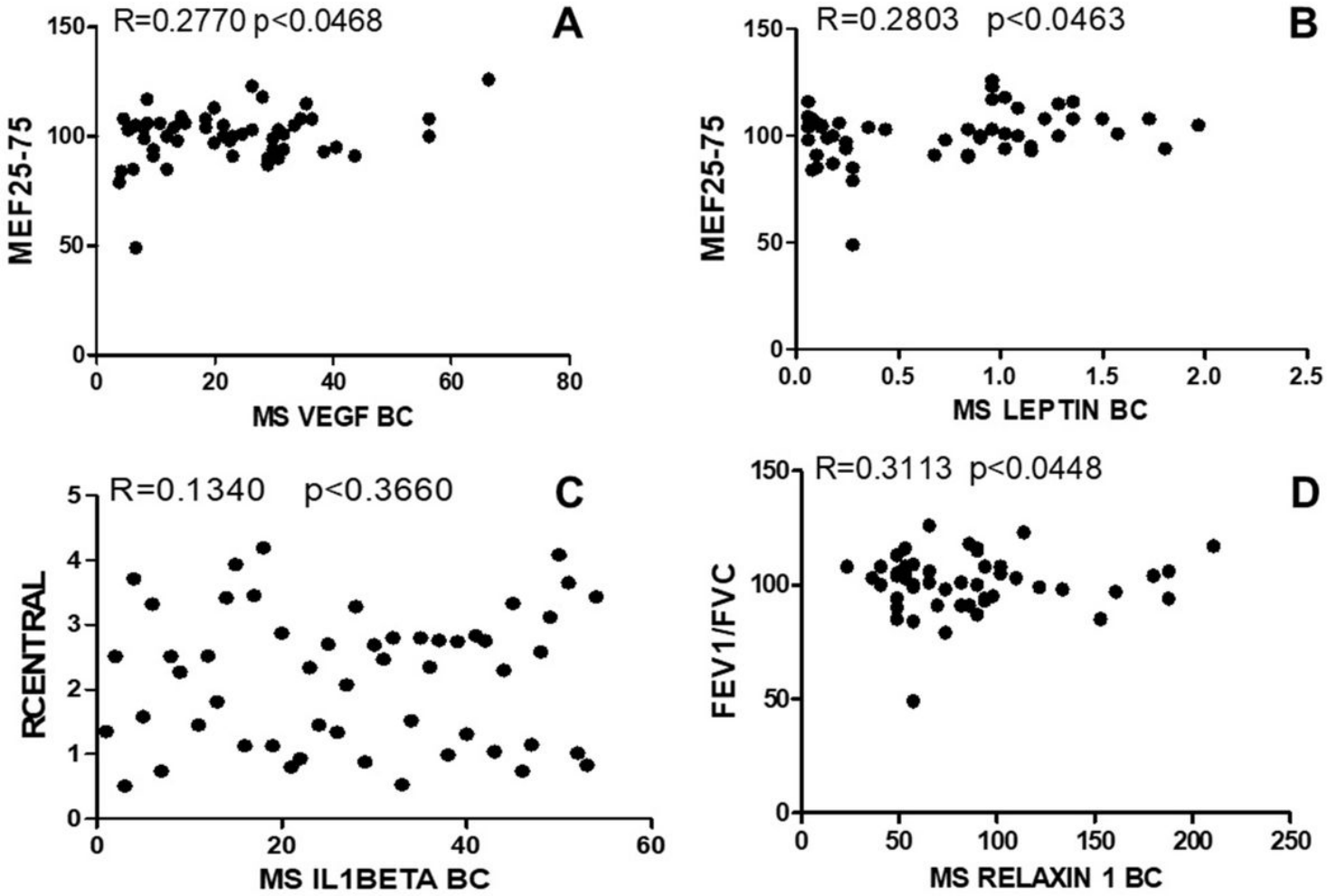

## Figure 3

Spirometric parameters for lung function from non-metabolic syndrome (NMS) and metabolic syndrome (MS) older adults. Figure 3A (FVC), Figure 3B (FEV1), Figure 3C (FEV1/FVC), Figure 3D (PEF), Figure 3E (MEF25), Figure 3F (MEF50), Figure 3G (MEF75).



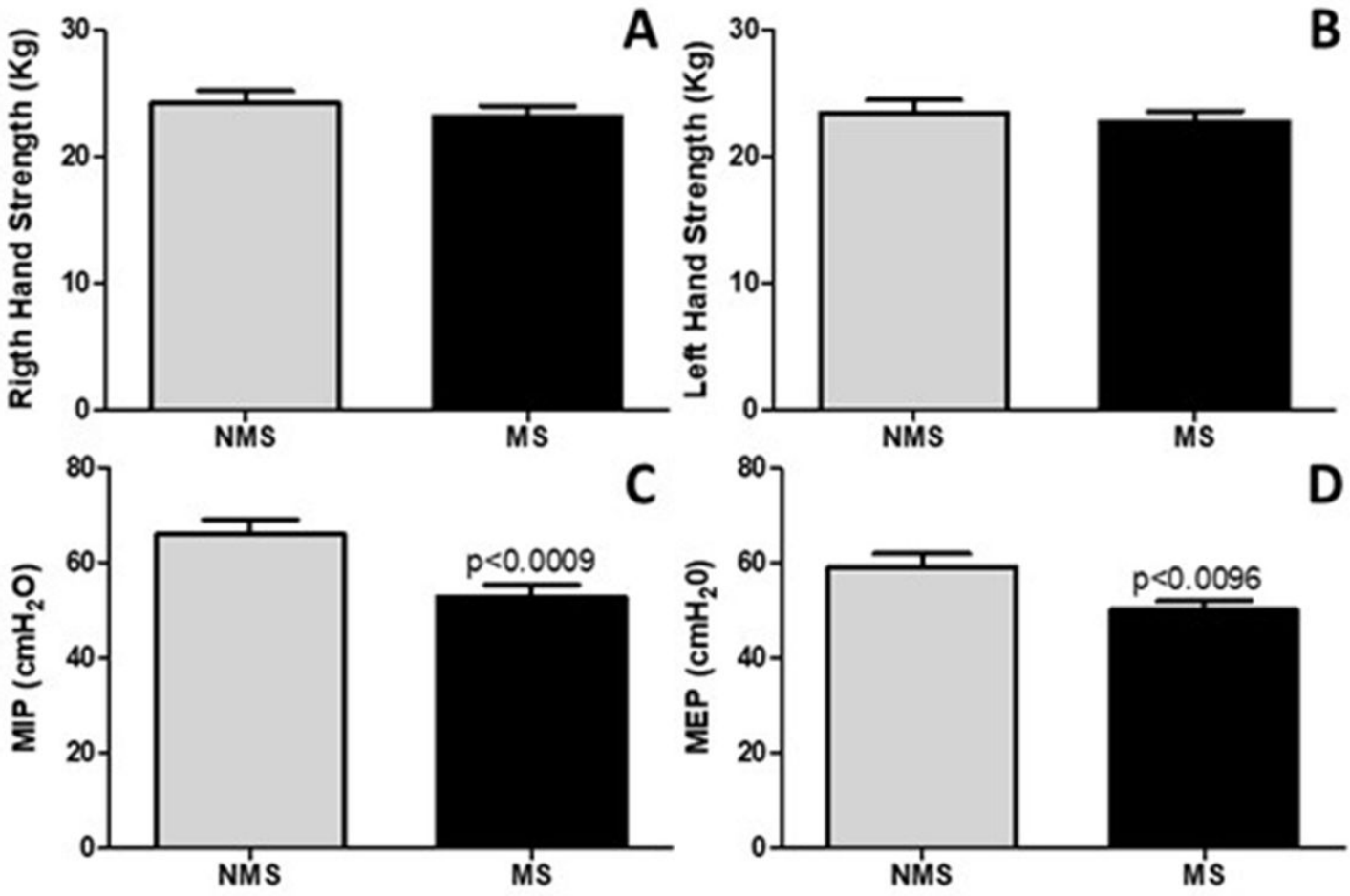

## Figure 4

Lung mechanics evaluated by impulse oscillometry (IOS) from non-metabolic syndrome (NMS) and metabolic syndrome (MS) older adults. Figure 4A (R5Hz), Figure 4B (R20Hz), Figure 4C (R5Hz-R20Hz), Figure 4D (X5Hz), Figure 4E (R Central), Figure 4F (R Peripheral).




## Figure 5

Correlation between pulmonary function, pulmonary mechanics and cytokines in breathe condensate: Figure 5A; R=0.2770; p<0.0468, MEF25-75 with the levels of pulmonary (breath condensate) of VEGF, Figure 5B; R=0.2803; p<0.0463 MEF25-75 with levels of pulmonary (breathe condensate) of Leptin, Figure 5C; R=0.1340; p<0.3660 RCENTRAL with levels of pulmonar (breathe condensate) of IL1BETA and Figure 5D; R=0.3113 p<0.0448 FEV1/FVC with levels of pulmonary (breathe condensate) of Relaxin 1




## Figure 6

General strength measured by hand grip strength and respiratory muscle strength measured by manovacuometer from non-metabolic syndrome (NMS) and metabolic syndrome (MS) older adults. Figure 6A (Right hand grip strength), Figure 6B (Left hand grip strength), Figure 6C (Maximal inspiratory pressure – MIP), Figure 6D (Maximal expiratory pressure – MEP).