Body composition, lung function, blood pressure, and muscular strength. A comparative study.

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Statement of Originality

I Roham Sadeghimakki, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Date……19/08/2019……..

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Abstract

Background: The loss of balance between components of body composition is significantly linked to a wide range of adverse clinical outcomes. Whilst the sharp rise in the rate of adiposity-based chronic diseases has caused substantial health concerns across the globe, sarcopenia has emerged as an important risk factor for increased morbidity and mortality among the aging population. Therefore, assessment of body composition phenotypes using the conceptual model of metabolic capacity and metabolic load enables an insightful evaluation of metabolic homeostasis association with health outcomes. Nevertheless, the evidence on such associations in the adult population is still lacking.

Objectives: To examine the relationship of anthropometric measures with total and segmental adiposity and muscularity; to investigate variations of blood pressure across body composition phenotypes; to explore the interaction effect of fatness and leanness on lung function, and to evaluate bidirectional association of lung function and blood pressure.

Study design and subjects: This project was a cross-sectional study of fifty healthy adults (22 men, 28 women) aged 19-65 years old. Anthropometric, body composition (Tanita MC-980 and InBody 720 segmental multifrequency bioelectric impedance analysers, and the BODPOD air displacement plethysmography system), blood pressure (OMRON M7 automated oscillometric monitor), grip strength (Takei 5001 analogue dynamometer) and spirometric (COSMED Quark PFT) measurements were carried out in Nutrition Physiology Laboratory at London Metropolitan University from 2016 to 2018.

Statistical analysis: Moderation analyses of the associations between body composition, blood pressure and lung function were conducted by the PROCESS modelling tool for SPSS

Results: None of the anthropometric measures were exclusively related to muscle mass. Neck circumference (NC) and upper arm circumference (AC) were the strongest and a body shape index (ABSI) was the only negative predictor of total and segmental muscularity in the entire population. Also, waist to height ratio (WHtR), waist circumference (WC), waist to hip ratio (WHR) and body mass index (BMI) were all strong correlates of total, truncal, visceral and upper arm fatness. None of the anthropometric measurements showed moderate or strong correlations with lower limb fatness. Fat mass (FM) to fat-free mass (FFM) ratio was only significantly associated with diastolic pressure (DBP) *(*β=17.6, p<0.001) whereas truncal FM (TFM) to appendicular skeletal muscle mass (ASM) ratio was associated significantly with systolic pressure (SBP) *(*β=15.94, p<0.01), DBP *(*β=27.47, p<0.001) and pulse pressure *(*β=-11.38, p<0.01). Stature-normalised truncal and appendicular adiposity (TFMI, AFMI) impaired lung function (FEV_1, FVC and $FEF_{25-75\%}$) respectively at high levels of truncal and appendicular muscularity (TSMI, ASMI). The negative impact of whole-body (high FM/FFM) and segmental (high TFM/ASM) metabolic overload on expiratory flow rate (FEV_1) was respectively conditioned on low DBP and high SBP *(*β=-.104, p<0.01, β=-.163*;* p<0.001). Negative effect of increased FM/FFM and TFM/ASM on FEV_1 and FVC was also operable at high levels of grip strength. There was a bidirectional association between lung function and systemic blood pressure. SBP and DBP were independently and negatively associated with FEV_1 *(*β=-.011 and -.019*;* p<0.001) and FVC *(*β=-.011 and -.022*;* p<0.001). FEV_1 and FVC demonstrated inverse associations with SBP (standardised β=-.38 and -.30; p<0.001) and DBP (standardised β=-.35 and -.40; p<0.001). Notably, the effect of FEV_1 and FVC on SBP was operated at higher levels of visceral adiposity whilst their influence on DBP was conditioned on higher levels of FFMI.

Conclusion: Whole-body and segmental metabolic homeostasis, pulmonary function and systemic blood pressure are complexly cross-linked. Therefore, phenotyping the individuals with or at risk of respiratory diseases and/or cardiometabolic disorders by their total and regional body composition, spirometric, and haemodynamic characteristics may result in more accurate risk stratification, personalised care and effective management strategies, leading to improved clinical outcomes, survival and quality of life.

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Abbreviations

6MWD	6-minute walk distance
ABCD	Adiposity-based chronic disease
ABSI	A body shape index
ADP	Air displacement plethysmography
AFM	Appendicular fat mass
AHA	American Heart Association
AHI	Apnoea-hypopnoea index
AHR	Airway hyperresponsive
AOI	Android to gynoid fat ratio
ASM	Appendicular skeletal muscle mass
ASMI	Appendicular skeletal muscle index
ASPEN	American Society for Enteral and Parenteral Nutrition
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BF%	Body fat percentage
BIA	Bioelectric impedance analysis
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BODE	Body Mass Index, Airway Obstruction, Dyspnoea, Exercise Capacity
BP	Blood pressure
BRC	Biomedical Research Centre
BSA	Body surface area
BTPS	Body temperature, pressure, saturated with water vapour
CC	Calf circumference
CF	Cystic fibrosis
CHD	Coronary heart disease
CI	Conicity index
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
Db	Body density
DBP	Diastolic blood pressure
DSM-BIA	Direct segmental multi-frequency BIA
DXA	Dual-energy X-ray absorptiometry
ECW	Extracellular water
EELV	End-expiratory lung volumes
EFL	Expiratory airflow limitation
EOT	End of test
ERK	Extracellular signal-regulated kinases
ERS	European Respiratory Society

ERV	Expiratory Reserve Volume
ESPEN	European Society for Clinical Nutrition and Metabolism
$FEF_{25–75\%}$	Forced expiratory flow between 25% and 75% of FVC
F_eNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FFM	Fat-free mass
FFMI	Fat-free mass index
FGF	Fibroblast growth factor
FM	Fat mass
FMI	Fat mass index
FRC	Functional residual capacity
FVC	Forced vital capacity
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IC	Inspiratory capacity
ICAM	Intercellular adhesion molecule
ICW	Intracellular water
IL	Interleukin
IMAT	Intermuscular adipose tissue
IR	Insulin resistance
KNHANES	Korean NHANES
LBM	Lean body mass
LFM	Lower limb fat mass
LLM	Lower limb lean mass
LLN	Lower limit of normal
LMI	Lean mass index
LSM	Lower limb skeletal muscle mass
LSMI	Lower limb skeletal muscle index
LVH	Left ventricular hypertrophy
MAMC	Midarm muscle circumference
MAP	Mean arterial pressure
MAPK	Mitogen-activated protein kinase
MCP	Monocyte chemotactic protein
MF-BIA	Multi-frequency BIA
MMPs	Matrix metalloproteinases
mMRC	Modified Medical Research Council
MUAC	Mid upper arm circumference
NBMI	New BMINC Neck circumference
NHANES	National Health and Nutrition Examination Survey
NHtR	Neck to height ratio
NIHR	National Institute for Health Research
OLS	Ordinary least squares
OR	Odds ratio
OSA	Obstructive sleep apnoea
PEF	Peak expiratory flow
PFSS	Pulmonary Functional Status Scale
PI3-K	Phosphatidylinositol 3-kinase
PP	Pulse pressure
PVW	Pulse wave velocity
QALYs	Quality-adjusted life-years

QoL	Quality of Life
RAAS	Renin angiotensin aldosterone system
RDI	Respiratory Disturbance Index
RR	Relative risk
RSNA	Renal sympathetic nerve activity
RV	Residual volume
SAA	Surface area artefact
SAD	Sagittal abdominal diameter
SBP	Systolic blood pressure
SDB	Sleep-disordered breathing
SEE	Standard error of the estimate
SEG-BIA	Segmental-BIA
SFA	Subcutaneous fat area
SGRQ	St. George's Respiratory Questionnaire
SMI	Skeletal muscle mass index
SMM	Skeletal muscle mass
SNS	Sympathetic nervous system
SO	Sarcopenic obesity
SP	Study participant
T2DM	Type 2 diabetes mellitus
TBW	Total body water
TC	Thigh circumference
TFM	Trunk fat mass
TLC	Total lung capacity
TNF	Tumour necrosis factor
TSM	Trunk skeletal muscle mass
TSMI	Truncal skeletal muscle index
UFM	Upper limb fat mass
ULM	Upper limb lean mass
USM	Upper limb skeletal muscle mass
USMI	Upper limb skeletal muscle index
UWW	Underwater weighing
VAT	Visceral adipose tissue
VC	Vital capacity
VFA	Visceral fat area
V_{TG}	Thoracic gas volume
WAT	White adipose tissue
WC	Waist circumference
WCR	Waist to calf ratio
WHO	World Health Organisation
WHtR	Waist to height ratio
Wt	Body weight
WTR	Waist to thigh ratio

Related Publications and Presentations

Sadeghimakki, R. and Mccarthy, H.D. (2019) 'The interaction effects of central adiposity, serum uric acid and vitamin D status on the systolic and diastolic blood pressure of adults with diabetes', 26th European Congress on 26th European Congress on Obesity. Glasgow, UK, 28 April – 01 May 2019: Abstracts, *Obesity Facts*, 12(suppl 1), pp. 180. doi:10.1159/000497797

Sadeghimakki, R. and Mccarthy, H.D. (2019) 'Anthropometric predictors of distal neuropathy in diabetic adults', 26th European Congress on 26th European Congress on Obesity. Glasgow, UK, 28 April – 01 May 2019: Abstracts, *Obesity Facts*, 12(suppl 1), pp. 184. doi:10.1159/000497797

Sadeghimakki, R. and McCarthy, H.D. (2019) 'Interactive effects of adiposity and insulin resistance on the impaired lung function in asthmatic adults: cross-sectional analysis of NHANES data', Annals of human biology, 46(1), pp.56-62.

Sadeghimakki, R. and McCarthy, H.D. (2017) 'Anthropometric predictors of high uric acid levels in adults with chronic kidney disease'. 4th UK Congress on Obesity, Pontypridd, Wales, September 7-8, 2017: Abstracts, UKCO2017 Programme Book - Association for the Study of Obesity. p42. Available at: https://www.aso.org.uk/wp-content/uploads/2018/07/Final-UKCO2017-Programme-Book.pdf

Sadeghimakki, R.; Mccarthy, H.D. (2016) 'The relationship between insulin resistance and pulmonary function in overweight or obese US adults with asthma. European Obesity Summit (EOS) - Joint Congress of EASO and IFSO-EC, Gothenburg, Sweden, June 1 – 4, 2016: Abstracts, *Obesity Facts*, 9(suppl 1), p. 83. doi: 10.1159/000446744

Problem Statement

Cardiovascular and respiratory diseases are leading causes of death and disability around the world. Annually, 3 million people die from chronic obstructive pulmonary disease. More than 25% of the world's population has high blood pressure while more than 300 million people suffer from asthma. Also, hypertension is the main modifiable risk factor for heart disease and stroke. Thus, hypertension and lung disease are substantial public health issues. Contemporaneously, the epidemic of obesity and the growing prevalence of sarcopenia have raised serious health concerns across the globe. Deviations from normal body composition and metabolic balance have been recognised as the important contributors to the development and/or worsening of cardiopulmonary disease; however, the mechanisms linking these entities are poorly understood and the complex cross-talk between body composition, respiratory capacity, and vascular function in health and disease warrants extensive research. The present research aims to probe these links using a phenotypic approach to provide an informative baseline for future exploration of the interactions among metabolic homeostasis and cardiorespiratory functioning in the general population.

Chapter 1

Introduction

Over a period of 50 years, the rapid pace of modernisation coupled with the advances in healthcare and standards of living have improved longevity and the quality of life across the globe. These advantages have been achieved at the cost of widespread lifestyle diseases. Such a broad range of chronic conditions may be caused or intensified by the potentiating interactions of excessively stored fat (obesity), as well as progressively diminished muscle mass and strength (sarcopenia), collectively termed "sarcobesity" (Parr, Coffey and Hawley, 2013).

1.1 Globesity

Obesity and being overweight, usually classified by a set of anthropometric measures, is now considered by many professional bodies as a chronic relapsing progressive disease arising from the pathologic alterations in the quantity, distribution and function of adipose tissue in genetically predisposed and/or environmentally influenced individuals, that can have a damaging impact on multiple organ systems, leading to a wide range of potentially debilitating complications (Jensen *et al.*, 2014; Frühbeck *et al.*, 2019). As demonstrated in the Diabetes Prevention Programme and Outcomes Study (DPPOS) and Look AHEAD (Action for Health in Diabetes) Trial, the long-term change in the body mass index (BMI) of the control groups with or at risk of type II diabetes who had elevated BMI levels at baseline was not significant. Besides, a large proportion of the weight lost in short-term in the lifestyle intervention groups was regained after a few years (Venditti *et al.*, 2008; Look AHEAD Research Group, 2013).

The rate of obesity has been rising sharply over the past few decades, making it one of the most important global public health issues of the new century. Since 1975, the

number of men and women with obesity has respectively increased by three and two folds. According to the latest World Health Organisation (WHO) report on obesity and overweight, approximately 40% of the world's adult population had excessive body mass in 2016, with obesity affecting more than 650 million adults over 18 years of age. The United Kingdom, with an obesity rate of 27%, ranks sixth in the world and is the second European country with the highest prevalence of obesity (OECD, 2017). In England alone, more than 60% and 50% of adult men and women have excess weight, respectively. The situation is similar in Scotland and Wales where more than one quarter of adults are obese (Conolly *et al.*, 2017). It is estimated that by 2025, 1 in 5 adults around the world will have obesity. A third of men and women living in the UK would probably be affected by this chronic condition if the present trend continues (Di Cesare *et al.*, 2016). Knowing this progressive ascent, it seems impossible to attain the targets set by the UN to stop global rise in obesity by 2025 (World Health Organisation, 2015).

Excessive adiposity exerts unfavourable effects on health, quality of life, and life expectancy of individuals. The most widely known co-morbidities of increased fat accumulation may fall into the following 10 domains: insulin resistance (IR) and type 2 diabetes (T2DM), cardiovascular disease (CVD), airway and pulmonary disease, gastrointestinal and liver disease, functional limitations, cancer, renal disease, musculoskeletal disorders, mental health status and body image. Among these, CVD and malignancies are the major contributors to the obesity-related mortality (Abdelaal, le Roux and Docherty, 2017). There is, however, a curvilinear relationship between commonly applied measures of obesity (body weight or body mass index) and a large proportion of adiposity-related pathologic states. Prospective Studies Collaboration report on the large-scale analyses of long-term follow-up data from almost 900,000 people demonstrated that, above the range of 22·5–25 kg/m² and adjusting for smoking, overall mortality as well as cause-specific mortality were significantly associated with overweight and obese categories of body mass index (BMI). For each 5-unit increase in BMI, all-cause mortality rose by approximately 30% while mortality from diabetic, renal, vascular, respiratory, and neoplastic causes increased by 120%, 60%, 40%, 20%, and 10%, respectively. Below this range, there was a strongly negative association between BMI and deaths from those causes except for ischaemic heart disease (MacMahon *et al.*, 2009).

Globesity would have inevitable impacts on the health and economy of the world. Given the above-mentioned trends, the projected health burden of the obesity epidemic in the UK and the USA by 2030 would add, on average, an excess of 7.2 million cases of diabetes, 6.5 million of coronary heart disease (CHD) and cerebrovascular accident (CVA), and more than 0.5 million cases of cancer, in addition to an average loss of 40 million quality-adjusted life-years (QALYs) in both countries combined. The healthcare expenditure attributable to adiposity-related conditions are projected to approach £2 billion excess annual spending in the UK by 2030 (Wang *et al.*, 2011).

From a clinical perspective, the term obesity is being replaced by the pathophysiologically more relevant, diagnostically useful and non-stigmatic term, adiposity-based chronic disease (ABCD) which conceptualises obesity as a chronic disease. This implies the longstanding disequilibrium between adaptive and maladaptive complex biological responses that underlie insidiously progressive derangements in the quantity, distribution, and functional status of body fat mass. Moreover, it avoids the ambiguities and inadequacies of a body mass index-centric definition of obesity and the stigma attached to it in the public domain (Mechanick, Hurley and Garvey, 2017).

Incorporating these three major features of adiposity into a complication-centric model creates a scientifically robust link between biological drivers of adiposopathy, their physical and non-physical contextual modifiers, and the adverse sequela of excess adiposity (Mechanick, 2016).

This new comprehensive approach promotes the application of anthropometric as well as more advanced body composition technologies (*e.g.* bioelectrical impedance analysis, air displacement plethysmography, hydrodensitometry, or dual-energy X-ray absorptiometry scan) in the evaluation of obesity (Garvey *et al.*, 2016).

1.2 Sarcopenia

Parallel to the rapid upsurge in the global rate of obesity and its complications, age-related decline in the quantity and quality of skeletal muscle, underpinned by the improved life expectancy and increased sedentariness, has emerged as a challenging

health concern which threatens the future of the ageing population all over the world. Given the ascending trend in the median age of the world's population, it is estimated that the number of elderly people would be tripled by 2050 (WHO, 2015b). As reflected in the Foresight report, the proportion of UK adults aged 60 and above will be growing steadily until 2040, amounting 22 million people (Foresight, 2016). In total, adults older than 40 may experience an average muscle mass loss of 40% and 1 to 3% annual decline in functionality over the course of their lives (Doherty, 2003; Toran *et al.*, 2012). The age-related progressive decline in skeletal muscle mass and strength, widely known as sarcopenia, is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as low muscle mass, low muscle strength and/or low physical performance based on sex-specific cut-off points (Cruz-Jentoft *et al.*, 2014). According to consensual definitions, worldwide prevalence of sarcopenia is about 10% in healthy men and women 60 years old and above (Shafiee *et al.*, 2017). In 2010, over 50 million people were estimated to be sarcopenic. This figure is projected to increase more than fourfold by 2050 (Cruz-Jentoft *et al.*, 2014). A secondary analysis of the Hertfordshire Sarcopenia Study (HSS) shows that 5 to 8% of free-living older adults in the UK are affected by sarcopenia (Patel *et al.*, 2013).

Sarcopenia imposes considerable burden on the health and well-being of the elderly. Primary(age-related) and secondary (activity, disease or nutrition-related) sarcopenia, especially combined with frailty and/or cachexia have deleterious impacts on morbidity, mortality, length of admission, quality of life, mobility, and physical performance of the individuals. Overall, sarcopenic individuals have 3 to 4 times higher adjusted risk of functional limitation, mortality, falls and fractures. Likewise, the length of hospital-stay and the incidence of hospitalization are increased 1.5fold in sarcopenic men and women (Beaudart *et al.*, 2017).

1.3 Sarcobesity

Deleterious effects of obesity and sarcopenia can compounded into a distinct phenotype called sarcopenic obesity (SO).Depending on the definition criteria, the age and gender adjusted prevalence of SO varies between 4 to 12% (Baumgartner, 2000; Zoico *et al.*, 2004). Reduced skeletal muscle mass and dysfunctional striated

muscle fibres coupled with the abnormalities in the number, size, distribution, and function of adipocytes can synergistically deteriorate physical functioning, cardiometabolic risk profile, and all-cause mortality of those with SO compared to individuals who are either obese or sarcopenic (Shao *et al.*, 2017). In the British Regional Heart Study, SO men older than 60 years (classified using waist circumference (WC) and midarm muscle circumference (MAMC) cut-offs), had significantly higher excess risk of all-cause mortality as compared to those with obesity, sarcopenia, and optimal WC and MAMC distribution, even after adjustment for lifestyle variables and established cardiovascular risk factors. Nevertheless, the risk of CHD or CVD was not elevated in this group (Davison *et al.*, 2002).

As a risk factor for hypertension, coexistence of low muscle mass and central adiposity seem to outpower sarcopenia or obesity alone. An analysis of Korea National Health and Nutrition Examination Survey (KNHANES) found that Korean adults with SO, defined by WC and the appendicular skeletal muscle mass (ASM) to body weight (ASM/Wt) ratio, had 6 times higher risk of essential hypertension than those without sarcopenia and obesity. Further, the chance of becoming hypertensive was 2 and 3 times higher in the sarcopenic obese phenotype compared with obese and sarcopenic phenotypes, respectively (Park *et al.*, 2013).

Sarcopenia is also a prevalent finding in patients with chronic obstructive pulmonary disease (COPD) with detrimental impact on their lung function, exercise performance, and cardiometabolic risk profiles. However, concomitant central obesity appears to counteract the negative effects of skeletal muscle loss and dysfunction on physical functioning and exercise capacity in the SO phenotype of COPD (Van De Bool *et al.*, 2015).

Given the critical role of deviations from normal body composition in the development, continuation, and deterioration of abnormal health conditions and morbid entities, it seems prudent to examine the main and interactive effects of fat mass (FM) and fat-free mass (FFM) on a wide array of health outcomes in the form of discrete body composition phenotypes and subclassifications. If applicable, these phenotypes should be defined according to age, sex, and ethnicity-specific cut-points as well.

In view of the recent shifts towards the integrated use of objective measures of adiposity and skeletal muscle dysfunction in the evaluation of lifestyle-related adverse end-points, many studies have used a phenotypic approach to investigate the influence of body composition status on musculoskeletal health, cardiometabolic health, aging, and survival rate in different subpopulations. (Waters *et al.*, 2010; Dufour *et al.*, 2012; Chung *et al.*, 2013; Rossi *et al.*, 2016). Nonetheless, these studies have been mainly conducted on geriatric groups and only few of them have addressed confounder-adjusted interaction of total and regional fat and lean mass on the baseline parameters of pulmonary and vascular function (Van Pelt *et al.*, 2002; Olsen *et al.*, 2005; Beckett *et al.*, 2010; Scott *et al.*, 2012; Park *et al.*, 2013, 2014). Also, there are scarce data on the compartmental contribution of body composition to the variations in health outcomes among otherwise healthy active young adults, especially in conjunction with their physical functioning. In addition, the influence of general, visceral, and appendicular body composition ratios over cardiorespiratory performance is still unexplored.

Aims:

To address the preceding gaps in the literature, the present research utilises body composition phenotyping of otherwise healthy adults in the context of a metabolic load – metabolic capacity model to elucidate the following topics:

- Differential utility of anthropometric measurements as the indicators of total and segmental body composition.
- Variations in measures of vascular function across body composition phenotypes
- The combined influence of total and regional fat and muscle mass on pulmonary function
- The role of systemic blood pressure and muscle strength in the association between metabolic homeostasis and respiratory physiology
- Metabolic homeostasis as a link between systemic blood pressure and lung function

Research hypotheses

1. Certain anthropometric measures can specifically correspond to total, truncal and appendicular adiposity or muscularity
2. Systemic blood pressure and arterial stiffness can be influenced by total and regional proportions of adipose and skeletal muscle tissues
3. Disparity between metabolic load and metabolic capacity may alter dynamic lung function
4. The effect of whole-body and segmental metabolic balance on respiratory capacity is modified haemodynamically
5. Respiratory and vascular systems are physiologically linked via shared mechanisms that are controlled by metabolic homeostasis

In the following chapter, an in-depth review of the extant literature on the implications of alterations in the quantity, distribution, and function of adipose tissue and skeletal muscle in health and disease is provided with an emphasis on the cardiovascular and respiratory systems. There, both observational and interventional studies are critically appraised in the matter of connections between obesity, sarcopenia, dynapenia, cardiorespiratory fitness and cardiometabolic health. Then, in chapter 3, there is a methodology of this cross-sectional research which utilises air displacement plethysmography (ADP), bioelectrical impedance analysis (BIA), anthropometry, dynamometry, spirometry, and sphygmomanometry to examine the abovementioned relations in a sample of active free-living adults. Thereafter, the results of descriptive and inferential analyses of the collected data are presented and critically discussed in chapters 4 to 7 to shed light on the application of total and segmental body composition phenotypes to the changes in pulmonary outcomes with an emphasis on the metabolic load- metabolic capacity model. Further, the modifying effects of blood pressure and muscle strength on the association of whole-body and segmental metabolic imbalance with respiratory capacity are probed. Finally, mutual relationships between systemic blood pressure and lung function are explored and the moderating role of adiposity and leanness are evaluated in chapters 8 and 9. It is not a purpose of this research to provide a detailed description of body composition models or the technical properties of measurement techniques applied to them. In the same way, fundamentals of respiration, spirometry, and the regulation of blood pressure are not thoroughly discussed. It is also worth mentioning that, from a body compositional perspective, this study mainly concerns fat mass and skeletal muscle mass. Therefore, the exploration of reciprocal changes in lung function and blood pressure in relation to the estimated hydration, protein, and mineral states are not the objectives of the current study. Moreover, the influence of fat mass and fat-free mass on the outcomes other than those pertinent to cardiovascular and pulmonary systems is beyond the scope of this research. This study does not intend to assess dietary intake and physical activity as the covariates of blood pressure and pulmonary function; thus, it does not include nutritional and activity data. Since this research does not employ dual-energy X-ray absorptiometry (DXA) scan or CT/MRI, direct measurements of visceral and subcutaneous adipose tissue are not included.

Chapter 2

Review of Literature

2.1. Body composition in health and disease

Body composition is an essential determinant of human health and a dynamic indicator of the nutritional status. Hence, the analysis of body composition plays a crucial role in the assessment of physiological as well as pathological states in both individuals and populations (Barr *et al.*, 2004; Kyle *et al.*, 2004a). The study of the components of body mass has been steadily gaining popularity in clinical practice, mostly due to the ongoing epidemic of obesity, increasing rate of lifestyle diseases, growing issue of age-related chronic conditions, and the emerging phenomenon of sarcopenic obesity which are directly or indirectly linked to over- and/or undernutrition. In a broader sense, malnutrition, as consensually endorsed by the European Society for Clinical Nutrition and Metabolism (ESPEN), and the American Society for Enteral and Parenteral Nutrition (ASPEN), is defined as a subacute or chronic inflammatory state of disordered nutrition in which the imbalance of energy, protein, and other nutrients adversely affects body composition, function, and clinical outcome (Jensen *et al.*, 2010). Thus, the assessment of body size, composition, and function in high-risk groups or malnourished people provides very useful information about the constituents of total body mass, broadly dichotomised as FM and FFM. Clinically, the assessment of nutritional status, fluid balance, bone mineral density, leanness, muscularity adiposity and energy requirement can be a cost-effective practically useful method for the nutritional and functional evaluation, identification and management of oedema, osteopenia, sarcopenia and/or obesity, outcome prediction and tailoring of medical treatment (Thibault and Pichard, 2012) in patients with a number of conditions, including frailty, pulmonary, cardiovascular, neoplastic, musculoskeletal, gastrointestinal, renal, and neurological diseases (Kyle and Pichard, 2000; Barbosa-Silva *et al.*, 2003; Kyle, Genton and Pichard, 2005; Prado *et al.*, 2008, 2011; Clark and Manini, 2010; Walter-Kroker *et al.*, 2011).

Such data can be applied in primary, secondary, and tertiary levels of care to predict health risks and gauge supportive measures and interventions accordingly (Soeters *et al.*, 2008, 2017). In light of recently decrypted molecular cross-talks between adipose tissue, skeletal muscle, bone and a plethora of biological abnormalities, the position of body composition measurement is strengthening in the diagnostic, therapeutic, and preventive strategies targeting a host of morbid conditions (Garvey, 2013; Mechanick *et al.*, 2013). This would entail more efficient decision-making about patients with a variety of comorbidities and at-risk populations as well as more satisfactory outcomes, and lower medico-economic costs (Guest *et al.*, 2011; Cefalu *et al.*, 2015). In this context, the feasibility and validity of total and segmental body composition analyses have been shown in large-scale population studies, including the UK Biobank imaging study, EU Childhood Obesity Program, German National Cohort, Korean Longitudinal Study of Healthy Aging and the National Health and Nutrition Examination Survey (GNC, 2014; Kim *et al.*, 2014; Luque *et al.*, 2014; Sudlow *et al.*, 2015; West *et al.*, 2016).

2.1.1. Overview of the models and methods of assessment

Since direct analysis of body compartments is only possible *post-mortem*, indirect techniques are employed to examine lean and fat tissues *in vivo*. There are many techniques available with varying degrees of accuracy, reliability, complexity, and feasibility, ranging from simple anthropometric measurements to sophisticated predictive methods. Because these techniques provide estimates of different aspects of body composition, all of them are subject to random and systematic errors and there is no single optimal method applicable to all conditions. Thus, a combination of methods are often jointly used to achieve greater accuracy(Wells and Fewtrell, 2006).

So far, several compartmental models have been suggested for the analysis of body composition. In the traditional two-compartment model(Welham and Behnke, 1942), the body is assumed to be made up of two chemically distinct compartments: fat mass (FM) and fat-free mass (FFM), possessing a constant density (0.9007 g/cm^3 and 1.100 g/cm^3, respectively) at 36°C. Due to the extremely difficult direct measurement of fat mass, FM is indirectly determined by subtracting total FFM

from body weight (Brožek *et al.*, 1963). This model is based on the measurement of total body density (Db) by hydrodensitometry or total body water (TBW) via isotopic dilution. Because this 2-component model was originally derived from the chemical analysis of cadavers, it did not separate out the nonessential extractible triglycerides stored in adipose tissue from the essential lipids (cholesterol, lecithin, and phospholipids) found in non-adipose structures (cell membrane, bone marrow, neural structures, and between myofibers) (Behnke, 1942). Ignoring the later portion that comprises 2.5% of the body mass in the conventional hydrodensitometry gives rise to the underestimation of FM. To distinguish the storage fat (adipose tissue) from the structural and functional fat, the terms lean body mass (LBM) or the triglyceride free mass (TGFM) have been proposed as conceptually more relevant alternatives to FFM (Withers, Laforgia and Heymsfield, 1999), although it is almost impossible to measure the essential lipids in living subjects (Mazzoccoli, 2016). Another limitation of this model is the inaccurate assumption of FFM constancy (0.723L/kg)(Pace and Rathbun, 1945). Unlike FM which has a relatively constant density, FFM density varies considerably with age, gender, race, hydration and nutritional status, and certain medical conditions(Withers *et al.*, 1998). To overcome these limitations, a three-compartment model was developed by Siri (Siri, 1961). This model subdivides FFM into TBW and fat-free dry mass (FFDM) that is composed of protein (and glycogen), osseous minerals (mainly calcium hydroxyapatite) and non-osseous minerals. It extends the previous model by combining underwater weighing (UWW) and deuterium dilution to measure body density and TBW. In this manner, the three-compartment model outperforms the basic one as it controls for the interindividual variability in the hydration fraction of FFM. However it assumes a constant ratio of mineral to protein (0.354) (Brozek and Henschel, 1961; Snyder, 1974).

Despite the theoretical influence of cumulative measurement errors arising from a larger number of body composition assessment techniques, this error (0.7% body fat percentage(%BF)) would not offset the excess accuracy gained by the three-compartment model, as it is much less than the propagated error pertinent to the classic two-compartment model (3.8%BF). Despite this improvement, it still fails to provide an accurate estimation of FM in those with protein depletion or low bone

mineral density (BMD) whose solid mass, and subsequently fat mass, would be incorrectly estimated(Withers, Laforgia and Heymsfield, 1999).

By contrast, a four-compartment model which includes DXA, obtains a direct measurement of bone mineral content (BMC) analogous to bone ash (Wahner *et al.*, 1985). This model is (at the molecular level) composed of FM, TBW, mineral, and residual (protein, non-bone minerals, glycogen, and the essential fat), thereby improving the accuracy of body composition analysis as it makes allowances for variations in bone mineral mass in addition to that of TBW and avoids the assumption of constant mineral to protein ratio. But the assumptions of protein, total mineral, and bone to non-bone mineral ratio constancy remain (Fuller *et al.*, 1992; Ellis, 2000). Nevertheless, the propagated error for the four-compartment model is equal to that of three-compartment model (0.7 %BF). Therefore, both models determine FM and FFM with acceptable precision and reliability(Withers, Laforgia and Heymsfield, 1999). A multicompartment 5-level model developed by Wang *et al.*, has generated a comprehensive framework which enables researchers to conduct body composition analysis in an organised and integrated fashion. This model clusters the compositional components of human body at five levels, namely atomic (body elements), molecular (BMC, fat, protein, and TBW), cellular (bone cell mass, extracellular water, extracellular solids, and fat), functional (skeletal muscle, adipose tissue, blood, bone, and others), and whole-body (FM, FFM) levels (Wang, Pierson Jr and Heymsfield, 1992). Hence, multicompartment profiling of body composition has enough accuracy to be considered the *in vivo* equivalent of carcass analysis and to act as the criterion method for the validation of other more frequently employed techniques(Wang *et al.*, 1993, 1998).

Notwithstanding the accuracy gained by the addition of compartments, impracticality (safety, complexity, availability, and expensiveness) of some methods used in multicompartment models *e.g.*, neutron activation analysis or whole-body counting) together with the propagated error of measurement attributable to the increased number of body composition assessment techniques limit their appeal. Furthermore, the comparison of three- and four-compartment models to multicomponent models in healthy adults have displayed a standard error of estimates <1% BF, implying that the incorporation of more components in the models of body composition measurement may not be so helpful in the clinical

setting (Wang *et al.*, 1998; Duren *et al.*, 2008; Kuriyan *et al.*, 2014). In the absence of a standardised method which can accurately merge all important components of body composition, nutritional assessment and risk estimation of various health related conditions would still be subject to uncertainty, inconsistency, non-expansiveness, as well as non-optimal specificity, predictive value, and clinical utility.

2.1.2. Bioelectric Impedance Analysis

Bioelectric impedance analysis (BIA) is the most frequently applied tool in body composition studies because it is a vastly available, non-invasive, convenient, quick, easy-to-handle, portable, and relatively inexpensive method.

In the contemporary BIA methods, the human body is thought to be formed of FM and FFM. FFM is usually considered to be composed of bone minerals and body cell mass (BCM) encompassing TBW and protein (including skeletal muscle mass (SMM))(Kyle *et al.*, 2004).

BIA measures body resistance (R) and reactance (X_c) against the flow of a low intensity alternating current. While R arises from extra-and intracellular fluids, X_c is caused by the capacitance of cell membranes. In fact, BIA determines body volume by means of resistance measurement. Based on the two-compartment model, FM is the non-conductive component of the human body whereas FFM is the conductor of electric current (73% of which is assumed to be TBW in euvolemic states). Thus, conductivity of the electrical current in biological systems is dependent on the electrolyte rich TBW as the compartment with the lowest resistance. Hence, components with higher fluid content (skeletal muscle) permit easier passage of the current. The impedance (Z), defined as the frequency-dependent opposition of a conductor (the body) to the flow of an alternating current (AC) circuit, is then calculated from the R and X_c.

Under basic assumptions of uniformity of surface area and homogeneity of composition, body volume (mainly TBW) can be proportional to body resistivity (ρ) and the conductive length (L) and inversely related to resistance(R): $V= \rho L^2/R$. This empirical relationship can be expressed as the impedance index ($height^2/R$),

substituting the conductive length (from wrist to ankle) by the more practically measurable height (Ht) (Rush *et al.*, 2013; Mialich, Sicchieri and Junior, 2014). However, the human body is neither a uniform cylinder nor an electrically isotropic conductor. Therefore, TBW (0.73* FFM) viewed as the conductive body volume, can be estimated in specific groups of subjects by using regression equations (validated against the reference methods) that include the impedance index (Ht^2/R). Then, FFM and FM can be predicted. The precision of this technique is inferior to that the criterion multicompartment methods.

Since 1987, a multitude of BIA equations for TBW, extracellular water (ECW), intracellular water (ICW), BCM, FFM, and FM have been published for various which also include age, anthropometric measurements, and constants of resistivity to improve prediction accuracy (Davies *et al.*, 1988; Deurenberg *et al.*, 1990; Houtkooper *et al.*, 1992). Nonetheless, standard error of the estimate (SEE) for these equations vary widely (0.7 to 12.3 kg, with the errors <3kg and 2.3 kg considered very good in men and women, respectively) (Houtkooper *et al.*, 1992).

BIA estimation of body composition suffers from several limitations. Because the experimental regression models relate to a certain reference population, validity of the estimations from these equations depends on a close match between the subject and the corresponding reference population, therefore, the BIA estimates for FM and FFM components are not generalisable. As mentioned before, the relation between body composition and impedance index is heavily modified by age, sex, ethnicity, anthropometric measurements, hydration, and health status (Houtkooper *et al.*, 1996; Ellis *et al.*, 1999; Mialich, Sicchieri and Junior, 2014). Age related dissociation between FM and FFM is a well-known phenomenon caused by gradual fat deposition (particularly visceral fat) and continuous muscle, body water, and bone loss. However, in advanced age, total fat mass tends to diminish due to the depletion of subcutaneous fat depots (Buffa *et al.*, 2011). Ethnicity is another source of bias in the impedance-based prediction equations for body composition. The SEE of TBW estimation by total and segmental BIA across ethnic groups varies with their corresponding body water distribution (ECW/TBW) and body build indices (arm span and leg length). Of note, total body impedance index has a higher correlation with TBW compared with segmental impedance indices (Deurenberg, Deurenberg-Yap and Schouten, 2002). There is an established sexual dimorphism in body

composition from childhood to late adulthood in a manner that females tend to have higher relative FM and lower relative FFM due to physiological and evolutionary reasons (Kirchengast, 2010). In addition, the accuracy of some reference methods used to develop many of these equations is questionable. For instance, densitometric methods make the incorrect assumption of FFM constancy. There have been inconsistencies in software versions used in the validation process too (Hofsteenge, Chinapaw and Weijs, 2015).

Bioimpedance measurement of body composition is conducted by two methods: whole-body BIA and segmental BIA. Whole-body bioimpedance analysers apply different arrangements of electrodes (hand to foot, hand to hand, and foot to foot) and various ranges of frequencies (single or multiple). Likewise, segmental BIA that views the body as five electroconductive cylinders (upper limbs, lower limbs, and trunk) uses different types of protocols for the attachment of voltage and current (unilateral dual current and quad voltage, bilateral dual current and quad voltage, and bilateral quad current and quad voltage) and two categories of frequency (single vs multiple). For a detailed review, please refer to De Lorenzo and Andreoli (De Lorenzo and Andreoli, 2003).

Owing to uneven cross-sectional area of the body, total body impedance is predominantly determined by the resistance of extremities (with smallest cross-sectional area). Consequently, whole-body BIA fails to adequately capture the changes in truncal FFM (skeletal muscle mass or BCM). For the same reason, it is not so sensitive to the intraabdominal fluid changes (Deurenberg, Deurenberg-Yap and Schouten, 2002). On the contrary, segmental-BIA (SEG-BIA) measures the phase angle (reactance/resistance ratio) of the trunk and extremities separately. This compensates for the lack of agreement between the resistance of trunk and the limbs in the whole-body bioimpedance measurements. Hence, SEG-BIA can be utilised as a reliable tool in the assessment of individuals with altered hydration status (Mialich, Sicchieri and Junior, 2014). Given the inverse association between the phase angle of the trunk and total body fat, segmental BIA performs significantly better in the prediction of %BF compared to whole-body method (De Lorenzo and Andreoli, 2003).

In comparison to DXA, however, SEG-BIA underestimates %BF in normal-weight and overestimates it in overweight/obese adults. SEG-BIA is superior to total body BIA in estimating whole body skeletal muscle volume (SMV) when cross-validated against MRI(Baumgartner, Chumlea and Roche, 1989). SEG-BIA can also predict FFM more accurately than whole-body BIA over a range of body shapes and muscularity states using ADP as the reference method(Kimberly J Shafer *et al.*, 2009).

There are also several nutritional, biologic, and technical factors that affect estimations by BIA, including previous exercise, dietary intake, posture, temperature, skin condition, geometrical properties and the arrangement of electrodes as well as measurement errors caused by motion, mispositioning, connector length and fabrication errors. There is considerable variability in the measurement of body composition between BIA devices too (a range of 1 to 8% has been reported for the coefficients of variation and SEE of BIA estimated TBW and FFM values, depending on the frequency, device, operator, and reference group)(Ishiguro *et al.*, 2005; Tanaka *et al.*, 2007). Thus, standardised protocols and regular calibration of the analysers and their components (signal generator, scale, sensors, and electrical interference) should be followed when undertaking BIA measurements (Kyle *et al.*, 2004).

In contrast, MF-BIA that uses a range of low and high (generally <20KHz and >50KHz) frequencies makes more accurate prediction of ECW than SF-BIA.(Patel *et al.*, 1996; Rikkert *et al.*, 1997; Simpson *et al.*, 2001). But it is not a sensitive indicator of transcellular fluid shifts in geriatric patients. In cross validation trials, SEEs of 5 to 8% have been reported for the estimation of TBW and ECW in healthy as well as overweight/obese adults (Bedogni *et al.*, 2002; Sartorio *et al.*, 2005). In a similar way, when validated against DXA, SEG MF-BIA underestimates %BF in the individuals at low levels of BMI (-1.56%) and overestimates it in those with high BMI (3.40%) (Kimberly J. Shafer *et al.*, 2009). It also fails to detect training-induced changes in FM and %BF (Sillanpää, Häkkinen and Häkkinen, 2013). Indirect measurement of truncal resistance by distally placed limb electrodes is another impediment to the accurate estimation of truncal body composition because of the unequal distribution of current in adjacent segments with dissimilar cross-section areas (Cornish *et al.*, 1999). This is contrary to direct and indirect resistance

measurements of the limbs which demonstrate high degrees of association by site and limb (Organ *et al.*, 1994). In addition, trunk resistivity is affected by altered hydration and fat distribution in the individuals with high levels of BMI. The reported estimation errors of %BF in obese people assessed by segmental MF-BIA are partly due to these factors (Medici *et al.*, 2005).

Despite these limitations, direct segmental multi-frequency bioelectrical impedance analysis (DSM-BIA) using the In-Body (720) body composition analyser which directly measures the impedance of trunk, arms, and legs at six different frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, 1000 kHz) has shown excellent agreement to DXA in the quantification of total FFM, FM and %BF (*ICC* ≥0.88) as well as segmental lean mass in the limbs (*ICC* ≥0.83) and good agreement in the measurement of truncal lean mass (*ICC* > 0.70) in middle-aged men and women from the Leiden Longevity Study. However, the limit of agreement for FM and %BF was wider than that of FFM. In this study, the overestimation of FM and underestimation of FFM was proportional to the rise in BMI (Ling *et al.*, 2011). Comparably, %BF and FFM estimated by DSM-BIA using TANITA MC780 displayed considerable correlation (*r*=0.85 and 0.98, respectively) and agreement (*ICC* =0.84 and 0.95, respectively) with measurements taken by DXA. in healthy young adults. However, visceral fat rating (VFR) was only a weak correlate of central fat percentage measured by DXA (Verney *et al.*, 2015). This index of visceral adiposity is highly dependent on the obesity status, underestimating visceral fat in those with BMI≤35 kg/m² and overestimating it at higher levels of BMI (Berker *et al.*, 2010). Therefore, DSM-BIA is an accurate method for the assessment of FFM, FM and %BF but not visceral fat in otherwise healthy adults, mainly with a normal range BMI.

In practice, BIA has many important diagnostic and monitoring applications because it allows the observation of fluctuations in body composition and detection of deviations of FM, FFM, and body fluids from the normal range. Furthermore, measurement of phase angle enables the healthcare professionals to accurately assess nutritional and clinical states of the individuals with a wide array of conditions. The most frequently BIA-examined bodily systems include pulmonary, cardiovascular, circulatory, musculoskeletal, gastrointestinal, renal, and neural systems (Bracco *et al.*, 1998; Cox-Reijven, Van Kreel and Soeters, 2003; Zlochiver

et al., 2007; Moreno, Djeddi and Jaffrin, 2008; Hoyle, Chua and Soiza, 2010; Cumming *et al.*, 2014). BIA has also been shown to be practically advantageous for the phenotypic classification of patients with COPD. Using the information from BIA, these patients can be divided into normal, overweight/obese but malnourished, cachectic, oedematous, and anorectic groups (Walter-Kroker *et al.*, 2011).

Taken together, modern BIA techniques can be regarded as reliable and accurate tools for the estimation of body composition in a wide variety of conditions. However, further research is required to specify the indications and cut-offs in different populations.

2.1.3. Air Displacement Plethysmography

Air displacement plethysmography (ADP) is a method for the assessment of human body composition that relies upon the calculation of body density to estimate body fat and fat-free mass. This system has been introduced as an alternative to the gold-standard hydrodensitometry (underwater weighing) because of the impracticality of the underwater weighing (UWW) in certain (elderly, children, severely obese, disabled) populations.

BODPOD is a commercially available whole-body air-displacement plethysmograph that determines body composition by calculating whole-body density(densitometry) under the same principles applied to the UWW. The only exception is that it measures the displacement of the air volume in the testing chamber instead of water volume to calculate body density (Db). The BODPOD is a two-chamber unit where the subject is seated motionless inside the front chamber while breathing normally. The unit is equipped with an electronically controlled diaphragm between the front and reference chambers that produces sinusoidal volume and pressure changes in both chambers. The computer attached to the unit then uses the body volume and body mass (measured by an accurate scale connected to the system) to calculate subject's Db, and subsequently, to estimate %BF, FM and FFM (Dempster and Aitkens, 1995).

Technically, this device determines the body volume based upon the pressure(P)/volume (V) relationship under adiabatic (labile temperature) condition.

This relationship is explained by the Poisson's Law as $P_1/P_2 = (V_2/V_1)^{\gamma}$ where γ is the ratio of the specific heat of the gas at constant pressure to that at constant volume (1.4 for air), V_1 and P_1 are the volume and pressure prior to subject entry into the test chamber and V_2 and P_2 are the volume and pressure while the subject is in the test chamber(Sly, Lanteri and Bates, 1990).

When utilising ADP, the effect of isothermal-like air close to body surface (air trapped within the fabric of clothing and the hair on the head and body) and isothermal air emanating from the lungs should be taken into consideration. This is because the isothermal gas is 40% more compressible than an equivalent volume of adiabatic air enclosed in the plethysmograph, resulting in a lower pressure output for a given body volume (Dempster and Aitkens, 1995). The interference of isothermal air with adiabatic air results in the overestimation of the air volume inside the BODPOD, and the underestimation of body volume. If uncorrected, this underestimation of actual body volume causes overprediction of Db and consequently underestimation of %BF (Fields, Hunter and Goran, 2000). To account for the effect of the isothermal air, thoracic gas volume (V_{TG}) is measured directly according to the following formula: V_{TG} = functional residual capacity + (0.5 × tidal volume) (Dempster and Aitkens, 1995). Because performing the breathing manoeuvre to measure intrathoracic gas volume is cumbersome for some groups of population, V_{TG} is sometimes estimated using validated prediction equations to predict FRC (Crapo *et al.*, 1982). Also, the surface area artefact (SAA) is automatically computed by the BODPOD's software as SAA(L) = k (L/cm^2) x BSA (cm^2), where k is an empirically derived constant of 1. BSA is the body surface area calculated from body weight and height according to DuBois formula. (Du Bois, 1989). V_{TG}-corrected Db is then used to estimate %BF (Siri, 1993). Although the estimation error is negligible, it may become an issue in very thin or extremely large individuals whose body size influences the magnitude of error (Fields, Higgins and Radley, 2005). Nevertheless, the BODPOD can accommodate subjects weighing 23 to 190 kg (Petroni *et al.*, 2003; Ginde *et al.*, 2005).

Environmental factors such as increased body temperature, body moisture, body hair, and clothing may increase the quantity of isothermal-like air surrounding the skin. Moisture retention may also be erroneously regarded as weight gain. In addition, the evaporation of water may change the correction constant γ (Higgins *et*

al., 2001). These sources of error may confound the estimation of %BF by up to 2% (scalp and facial hair may result in 2 and 1% underestimation of %BF while clothing can lead to 2-5% error in the estimation %BF)(Higgins *et al.*, 2001; Hull and Fields, 2005).

The validity of this instrument has been tested against the reference methods of body composition assessment in different clinical conditions and several groups of individuals. In an adjusted regression analysis of two birth cohort studies at 18 and 30 years, BODPOD-estimated FM and FFM were found to be the oppositely directed significant of the absolute FEV_1 and FVC in Brazilian adults. These changes in FEV_1 and FVC were larger than those estimated by DXA-measured FM and FFM in both follow-up groups (De Oliveira *et al.*, 2016). In patients with moderate-to-severe COPD, ADP-determined FFM has been shown to be clinically useful in detecting lean mass depletion (Flakoll *et al.*, 2004).

Across levels of BMI, the BODPOD has been shown to overestimate %BF by approximately 6.8% in the underweight group compared to DXA. In the normal-weight group, the BODPOD tends to overestimate %BF by approximately 2% whereas in the overweight/obese group it underestimates %BF by 3% (Lowry and Tomiyama, 2015). In contrast, no significant between-method difference in Db measurements (0.001 to 0.002g/cm^3) and no %BF estimation bias has been found for ADP and UWW. %BF estimates from UWW and ADP were also strongly correlated (r=0.94, SEE= 3.58%) in overweight and obese adults (Ginde *et al.*, 2005). In a study of middle-aged healthy white men, Sardinha *et al.* showed that the precision of Db measurement by ADP on repeated trials was comparable to that of UWW (trial-to-trial variation ≈ 0.0020 kg/L). In contrast, the researchers observed that ADP underestimated %BF compared to DXA (2.6 ± 2.7%). In addition, adjusted multiple regression models that used ADP estimates of %BF, FM, and FFM had greater predictive ability (highest r^2 and lowest SEE) against the corresponding DXA measured parameters as compared to other models of body composition assessment (Sardinha *et al.*, 1998). Concurrent validity of the BODPOD and DXA in determining %BF has also been supported in white college-aged women (24.3 ± 1.1% versus 23.8±0.8%) (Maddalozzo, Cardinal and Snow, 2002).Validity and reliability of the BODPOD in determining %BF has also been confirmed against UWW in a heterogenous sample of adults from different age, ethnic and fatness

groups (test-retest coefficient of variation=1.7±1.1% and mean difference= -0.3± 0.2%)(McCrory *et al.*, 1995). However, BODPOD overestimated %BF by 1.9% and 1.6% compared with UWW and DXA in a sample of young black men (Wagner, Heyward and Gibson, 2000). Moreover, ADP and DXA may not be used interchangeably for the assessment of FFM in the community dwelling older adults, as their limits of agreement exceed the maximum allowed difference between methods (95% LOA -11.0 to 2.4 kg in males and -4.8 to 2.2 kg in females) (Bertoli *et al.*, 2008). Nonetheless, a study of free-living elderly men and women reported no significant difference between Db measurements by ADP versus UWW (Yee *et al.*, 2001).

These discrepant findings may be due to dissimilarities in measurement protocols (separated measurements of lung volume and body volume, predicted versus measured calculation of lung volume), test equipment, software version, test conditions (clothing, moisture, metabolic rate), V_{TG} prediction, estimation inaccuracies inherent in the models, gender, body size, and food or drink ingestion(Fields and Goran, 2000; Wells *et al.*, 2003).

Compared to other techniques, ADP is less time-consuming, easier to operate, and more convenient, making it a favourable tool applicable to a broad range of population. Furthermore, it is more feasible for obese individuals whose large body size limits the use of other instruments (scanning area in DXA, seat size in hydrostatic weighing, weight-recording potential of the footplate in BIA).

2.2. Spirometry

Spirometry is a valuable physiologic test for the assessment of respiratory health in public health and clinical settings. It's been globally employed by researchers and healthcare professionals for epidemiological, diagnostic and monitoring purposes. Basically, spirometry measures the flow and volume of air (litre) exhaled during the forced expiratory manoeuvre as a function of time (seconds). These measurements are graphically displayed as volume-time and flow-volume curves in the spirogram. Due to laminar characteristics of the expiratory flow inside the airways, flow rate is determined by the Hagen–Poiseuille equation: $Q = \pi r^4 \Delta P / 8\eta l$, where P is the

pressure drop in the air moving along the continuum of a tube of certain length (l), radius(r), and viscosity (η) (Sutera and Skalak, 1993).

The most widely used parameters of the spirometric test include the forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC%), and the mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$). FVC is the maximum volume of air delivered during a forceful and complete expiratory effort (lasting 6 seconds) following a maximal inspiration. FEV_1 is the maximal volume of air exhaled in the first second of a forced expiration starting from full inspiration. Both spirometric indices are expressed in litres at BTPS (body temperature, pressure, saturated with water vapour) condition. In healthy individuals, FEV_1 comprises about 70-80% of FVC (FEV_1/FVC%). $FEF_{25–75\%}$ also known as the maximum mid-expiratory flow is derived from the blow with the greatest sum of FVC and FEV_1 (Levy *et al.*, 2009).

Spirometers are usually divided in two categories: volume sensing devices and flow-sensing spirometers. Volume displacement spirometers calculate the airflow by directly measuring the volume of the expired air based on the movements of a bell (water seal), piston (dry rolling seal) or bellows in response to breathing excursions. The wet (water-seal) spirometer consists of a counterweighted rigid cylinder (bell) inverted into a water tank. Water creates an airtight seal between the two containers. Vertical displacement of the cylinder through the respiratory cycle is conveyed to the recording device. Because of the inertia of the moving parts, wet spirometer suffers from a lag time which means the initial portion of the expired breath would fill the dead volume of the cylinder and would not be measured. Therefore, the accuracy of this instrument is lost at higher respiratory flow rates, particularly during FVC manoeuvre, making it clinically less useful. A dry (rolling-seal) spirometer is practically more convenient and consists of a piston moving horizontally in a larger cylinder. A U-shaped rolling diaphragm between the two parts provides the seal and minimizes the friction. The volume is recorded by a sensor that detects horizontal displacement of the piston. In the bellow-type spirometer, the volume changes of the exhaled air are transferred to a recording scriber via expansion of the wedge-shaped bellows. As this instrument produces a

volume-time curve, it can measure forced expiratory volume and flow rates in a single vital capacity breath(Mandal, 2006).

These traditional types of spirometers, however, have been largely supplanted by flow-sensing spirometers because of their smaller size, easier operability, maintenance, and cleaning and even their compatibility with disposable sensors. These modern devices calculate the exhaled volume from the flow rate information recorded by various flow transducers, i.e., turbines(respirometer), pressure-differential sensors(pneumotachometer), heated-wire sensors(anemometer), and ultrasonic sensors(Gibbons, 2004).

Pneumotachographs measure rapidly changing flow rates of the inspiratory and expiratory air based on the variable pressure changes across a resistive element (Hagen–Poiseuille relationship) that are sensed by a differential manometer. Tubular configuration of this flow meter maintains the laminarity of the air stream while the heating system prevents condensation and ensures constancy of the gas temperature. These arrangements make pneumotachographs sensitive and accurate pieces of equipment.

Anemometer measures flow rate of the expired air from the temperature drop in an electronically heated (platinum) wire induced by the cooling effect of the flowing air. Changes in the exhaled gas temperature, humidity, and composition are compensated by appropriate corrections. This instrument is sensitive and accurate(Mandal, 2006).

Respirometers are the most commonly used spirometer in the clinical setting. Present-time turbine spirometers are equipped with deflector endplates which spiral the airflow that travels through the body of the turbine, rotating a vertically placed vane. Vane rotations are counted by the optical sensors and are used to measure the volume of the flowing gas. Flow rate is then derived from the recorded volumes over time. Although the sensors are relatively insensitive to the variations in gas composition, water vapour and altitude (Pedersen *et al.*, 1994), the accuracy of the turbine flowmeter may be affected by friction, inertia, vane area, and the efficiency of deflectors at the extremes of flow rate spectrum. Wide intervals of agreement in peak expiratory flow (PEF) and FEV_1 measurements have been reported between turbine and pneumotachograph spirometers. Under-reading occurs at low tidal

volume whereas over-reading happens at high tidal volume or high peak flow (Jones and Mullee, 1995). These factors should be corrected by the software supplied with the respirometer. In a multi-centre comparative study of the office and standard spirometers of various types, all spirometers were shown to be comparably precise in measuring FEV_1 (upper limits of precision fixed at 200ml); however, proportional bias was reported for small turbine flowmeters at lower and higher values of FEV_1. In addition, small spirometers had poor FVC repeatability (>200ml) and broad levels of agreement with standard spirometers for FEV_1 (>350ml) and FVC (>500ml) (Liistro *et al.*, 2006).

Spirometric parameters are usually recorded during forced expiratory manoeuvres. The manoeuvre consists of three phases: 1) maximal inspiration; 2) forceful exhalation; and 3) continued complete exhalation to the end of test (EOT) when the subject cannot carry on with the forced expiration any further or the volume–time reaches a plateau(volume changes <0.025 L) that lasts ≥ 1s after an expiratory effort of ≥3s (in children) or 6s (in adults). Although, prolonged exhalation (>6s) is commonly observed in older people or those with airway obstruction. This sequence of events is also graphically captured in the flow-volume curve as a steep rise in the expiratory flow followed by a gradual decline until the EOT. It is worth noting that the test should be terminated at the first indication of discomfort, dizziness, or imminent syncope (Bellamy and Booker, 2005). As maximal expiratory volume and flow values are highly effort dependent, standard procedures should be carefully observed to minimise the variability in measurements (please refer to chapter 3 for a detailed description of the FVC protocols, pre-test instructions, and prompts given by the operator during the test).

Although the FVC manoeuvre can be performed in the sitting or standing position, the former may lead to lower vital capacity in middle-aged and centrally obese individuals. Nevertheless, for safety reasons, an upright sitting position is preferred in the elderly. Tendency to lean head and trunk forward towards the end of forced expiration should be discouraged as it may lead to tracheal compression and the accumulation of saliva in the mouthpiece (Quajer *et al.*, 1993).

An adequate spirometry requires three acceptable FVC manoeuvres out of maximum 8 attempts (to reduce breath-to-breath variations and to prevent fatigue) meeting the

following criteria: absence of artefacts (coughing in the first second of expiratory effort, Valsalva manoeuvre, early termination, partial expiration before connecting the mouthpiece, submaximal attempt, mouthpiece obstruction by tongue, teeth or lips, leak, extra breath), good start (automatically back-extrapolated volume, <5% FVC or 0.150 L), no hesitation at full inspiration (<2s), satisfactory exhalation (≥6 s for subjects>10 years, ≥3s for children <10 years) or a plateau in the volume–time curve). Repeatability of these acceptable attempts should also be ascertained (no greater than 0.150 L difference between the two largest values of FVC as well as FEV_1) (Quajer *et al.*, 1993). Figure 2.1 summarises the stepwise application of the criteria.

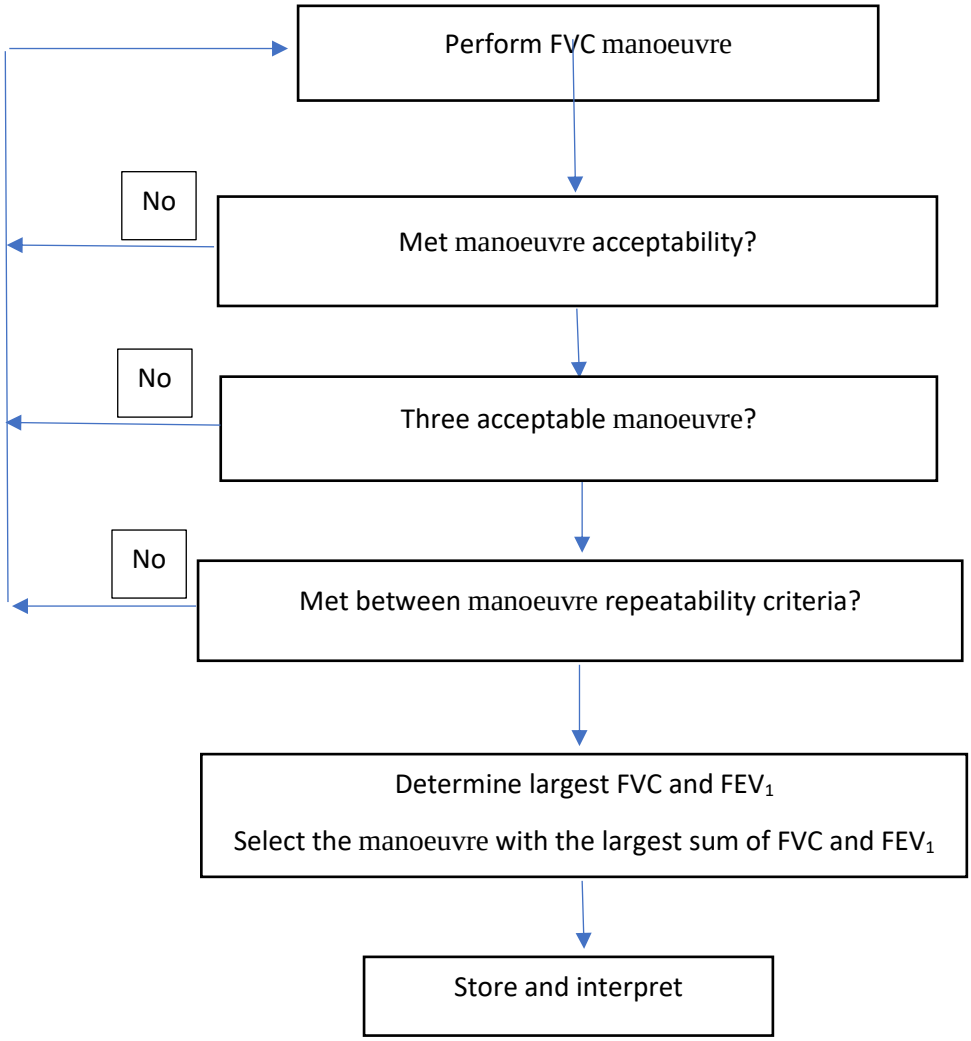


Figure 2.1 Flow chart outlining how acceptability and repeatability criteria are to be applied. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second (Miller *et al.*, 2005, p 326)

Biological variability is another source of error in the spirometric measurements. Factors such as sex, age, ethnicity, posture, physique, diurnal variation, exposure to airway irritating substances (tobacco, inhalants, allergens, pollutants, drugs), and respiratory pattern may influence the accuracy and precision of lung function tests (Miller, Hankinson, *et al.*, 2005).

The accuracy of a spirometry system is also considerably affected by the internal characteristics of the equipment and the environmental conditions. This requires regular quality-control and calibration checks to ensure the volume accuracy (±3.5% using a 3-L calibrated syringe discharged daily), absence of leaks (<30 ml volume loss upon application of constant pressure 3.0 cmH_2O for 1 minute), linearity (tested weekly with a 3-L syringe by delivering relatively constant flows at low, mid, and high- flow ranges, with an accuracy requirement of ±3.5% at each range), and time-scale accuracy (±2% assessed quarterly with a stopwatch). In addition, the differences between the ambient temperature and pressure (ATP) and the BTPS (condition in the lungs) should be accounted for by the appropriate BTPS correction factors when recording expiratory volume and flow measurements (Quajer *et al.*, 1993; Miller, Hankinson, *et al.*, 2005). Table 2.1 shows a summary of the American Thoracic Society and the European Respiratory Society ATS/ERS task force recommendations on the standardisation of lung function testing.

Table 2.1 Recommendations specified for forced expiratory manoeuvres (Miller *et al.*, 2005, p 332)

Test	Range/accuracy (BTPS)	Flow range ($L.s^{-1}$)	Time (s)	Resistance	Test signal
FVC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0–14	15	1.5 $cmH_2O.L^{-1}.s^{-1}$	24 ATS waveforms, 3-L Calibration Syringe
FEV_1	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0–14	1	1.5 $cmH_2O.L^{-1}.s^{-1}$	24 ATS waveforms, 3-L Calibration Syringe
PEF	Accuracy: ±10% of reading or ±0.30 $L.s^{-1}$, whichever is greater; repeatability: ±5% of reading or ±0.15 $L.s^{-1}$, whichever is greater	0–14		Mean resistance at 200, 400, 600 $L.min^{-1}$ (3.3, 6.7, 10 $L.s^{-1}$) must be ,2.5 cmH2O. $L^{-1}.s^{-1}$	26 ATS waveforms
$FEF_{25-75\%}$	7L ±5% of reading or ±0.20 $L.s^{-1}$, whichever is greater	±14	15	Same as FEV_1	24 ATS waveforms

BTPS: body temperature and ambient pressure saturated with water vapour; FVC: forced vital capacity; ATS: American Thoracic Society; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; $FEF_{25-75\%}$: mean forced expiratory flow between 25% and 75% of FVC

There are also certain conditions where performing FVC manoeuvre may be absolutely or relatively contraindicated (Levy *et al.*, 2009). Please refer to Chapter 3 for a detailed description of these conditions.

Based on the spirometric curves, three distinct patterns are recognisable: normal, obstructive and restrictive. The FEV_1/FVC ratio and a subsequent FVC are used to distinguish between the abnormal spirometric patterns. While a reduced value represents an obstructive ventilatory pattern, a normal/increased ratio is indicative of a restrictive pattern. It is not uncommon though to observe a mixed pattern of

ventilatory abnormality(Pauwels *et al.*, 2001). An extensive review of the diagnostic guidelines (Pellegrino *et al.*, 2005) is beyond the scope of this research.

Until recently, percent predicted values were widely employed to define the low values of spirometric indices. These values were derived from the reference linear regression equations including sex, age, height and ethnicity. For adults older than 18 years, cut-offs of 0.7 (FEV_1/FVC) and 80% predicted (FVC) were recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as the diagnostic thresholds for obstructive lung defects (Fabbri and Hurd, 2003). It should be remembered, however, that the assumptions of linearity and homoscedasticity are not met in these prediction equations in different combinations of age and height, particularly for FEV_1 values, leading to systematic underestimation of the predicted values and large variability in the reported reference values. As the predicted residuals are disproportional to the predicted values, considering a fixed percent predicted value as the lower limit of normal (e.g., 80% implying 20% deviation from the predicted normal value) would result in the misinterpretation of the spirometry data (Stanojevic *et al.*, 2008; Miller *et al.*, 2011). These non-linear relationships can be captured by adding splines that correct for the age-specific predicted values (Rigby and Stasinopoulos, 2005; Pistelli *et al.*, 2007). Moreover, adopting a fixed FEV_1/FVC cut-off (0.7) for diagnosing airway obstruction does not account for the age and height-related declines in FEV_1/FVC ratio (including the healthy lifelong non-smokers), leading to over-diagnosis in the elderly and under-diagnosis in young subjects (Quanjer *et al.*, 2011).

The ATS and ERS have instead supported the recommendations of Global Lung Function Initiative (GLI-2012) to define lower limit of normal (LLN) by Z-scores. LLN represents the 5^{th} percentile (1.64SD below the mean) of spirometry data obtained from the reference healthy non-smoking population (for the ATS criteria, it is derived from the Third National Health and Nutrition Examination Survey (NHANES III)). GLI-2012 reference equations adjust for the age, height, gender and ethnicity-dependent coefficients of variation in the predicted spirometric indices and smooth out the non-linear regression curve by including a spline. Further, using Z-scores standardises the residuals of these predicted indices, making the LLN-based interpretation of PFT results independent of the abovementioned covariates (Quanjer *et al.*, 2012). Importantly, lung function, respiratory performance and pulmonary

health are anatomically, physiologically and metabolically linked to the body composition. Alterations in the quantity, distribution, and functional attributes of the lean and fat mass exert significant direct and indirect influences over lung function.

The purpose of the next sections is to review the existing evidence on the effects of fatness and leanness on the respiratory physiology in adults under normal and abnormal conditions.

2.3. Body Composition and Lung

2.3.1. Adiposity and lung physiology

Adipose tissue influences several aspects of lung physiology including lung volume, respiratory mechanics, airway function, ventilation and gas exchange. Truncal fat accumulation mechanically distorts the balance of inward and outward elastic forces effected by the lung and the chest wall, leading to diminished functional residual capacity (FRC), i.e., the volume of air remaining in the lungs after a normal tidal expiration (Pelosi *et al.*, 1998). FRC decreases exponentially with BMI, tapering off to the residual volume (RV), the volume of air left in the lungs after a maximal expiration, at the extremes of BMI (Jones and Nzekwu, 2006). In contrast, the effect of fat mass on the RV is negligible, especially in men (Watson, 2004) whereas total lung capacity (TLC) is modestly affected by the changes in BMI and fat distribution(Collins *et al.*, 1995). Although the space-occupying effect of intrathoracic fat may reduce TLC (Watson *et al.*, 2010), the impeded descent of the diaphragm is thought to be the primary mechanism underlying the TLC-lowering effect of central adiposity (Salome, King and Berend, 2010). Since the RV and TLC are not markedly affected by excessive adiposity, FRC reduction in overweight or obese individuals is mainly due to the marked reduction in the expiratory reserve volume (ERV), i.e., the additional volume of air that can be exhaled forcefully after a normal tidal expiration (Jones and Nzekwu, 2006).

Anatomical location of fat depots also plays a modifying role in the associations between fatness and lung volume. As opposed to the lower body fat which has not been shown to be an important contributor to the altered lung volume in the

individuals with higher BMI, upper body fat exhibits inverse relationships with FRC and ERV in adults of both genders (Canoy *et al.*, 2004; Chen *et al.*, 2007). MRI-quantified visceral and anterior subcutaneous (rib cage and abdominal) fat have been found to be significant correlates of lower end-expiratory lung volumes (EELV) in overfat adults as compared to those with normal fatness (Babb *et al.*, 2008). Thus, the association of BMI with the components of lung volume is mediated by the cumulative effect of thoracic and abdominal fat. These fat depots make comparable contributions to reduced TLC, FRC, and ERV in adults (Sutherland *et al.*, 2008).

The absolute static lung compliance, defined as the volume changes in lungs per unit changes in transpulmonary pressure (the slope of pressure-volume curve), also appears to decline exponentially with the incremental changes in BMI (Pelosi *et al.*, 1998). This could be due to the reduced lung volumes, deposition of subcutaneous fat on the plural surfaces and chest wall with subsequent overloading of the respiratory muscles, increased pulmonary blood volume and congestion of bronchoalveolar vessels followed by the narrowing of the small airways, and the increased alveolar surface tension caused by FRC reductions (Rubinstein *et al.*, 1990). Nevertheless, mixed results have been reported on the impact of obesity on chest wall compliance. While several studies have not found significant differences between obese and non-obese individuals in various postures and levels of consciousness (Sharp *et al.*, 1964; Hedenstierna and Santesson, 1976; Suratt *et al.*, 1984), chest wall and lung compliance were found to be lower in sedated postoperative morbidly obese patients as compared to normal weight subjects (Pelosi *et al.*, 1996).

Lower EELV (in the presence of an unchanged RV) and reduced lung compliance of individuals with excessive adiposity lead to tidal airway closure and expiratory airflow limitation (EFL), particularly in the supine position. These, in turn, increase the risk of air-trapping in lung bases, peripheral airway injury (obstruction), maldistributed ventilation, and impaired gas exchange (Milic-Emili, Torchio and D'Angelo, 2007).

Other than lung compliance, airway resistance is also affected by the excessive adiposity. Notably, male individuals with high BMI have more resistant airways than those with normal BMI. This relationship can be partly explained by low lung

volume, reduced FRC, narrower and remodelled airways, and intrathoracic lipid deposition (Inselman, Wapnir and Spencer, 1987; Salome, King and Berend, 2010). By reducing FRC, truncal adiposity removes the mechanical restraints against the hypercontractility of airway smooth muscles. Furthermore, breathing at lower tidal volumes impairs the bronchodilating effect of normal tidal strain on these smooth muscles, accentuating airway hyperresponsiveness in individuals with obesity (Shore and Fredberg, 2005).

In addition to lower airways, the upper respiratory tract is also influenced by the abnormally accumulated fat around the pharynx (reflected in the increased neck circumference) and torso. Deposition of adipose tissue in these areas reduces the calibre of the upper airways. This mechanical load together with and lower lung volumes predispose the individuals with obesity to pharyngeal collapsibility, upper airways narrowing and sleep apnoea (Schwartz *et al.*, 2008). Moreover, release of pro-inflammatory cytokines from the abnormally expanded (visceral) adipose tissue blunts the central and peripheral compensatory neuromuscular responses to the altered structure and function of upper airways (Schwartz *et al.*, 2009)

In the upright position, , the optimal ventilation occurs at the lower dependent lobes of normal-weight individuals whereas the gradient of ventilation can be reversed in the individuals with excessive adiposity due to the occlusion of small airways, leaving the lower zones of the respiratory system under-ventilated in this group of people (Demedts, 1980). Concurrently, the pulmonary blood supply is predominantly distributed to the lower lobes, creating regional ventilation-perfusion (V/Q) mismatch in the misconfigured lungs of the obese individuals with low ERVs, particularly in the sitting and lateral decubitus positions (Holley *et al.*, 1967). V/Q mismatch then gives rise to the widening of the alveolar-arterial oxygen (A-aO2) gradient (>15 mmHg) and, in the morbidly obese subjects, hypoxemia (P_aO_2<80mmHg) (Hakala *et al.*, 1995; Pelosi *et al.*, 1998) that may improve after bariatric surgery (Thomas *et al.*, 1989). In fact, measures of central adiposity, *i.e.*, waist to hip ratio (WHR) and WC have been found to be significant predictors of the A-aO_2 gradient and PaO2 before and after weight loss, with larger effects in men and in the supine position (Vaughan, Cork and Hollander, 1981; Zavorsky *et al.*, 2007).

Maintenance of a proper match between perfusion and ventilation, and consequently, unabated pulmonary gas exchange in individuals with overfatness during exercise is the result of the overactivity of respiratory musculature (Babb, Buskirk and Hodgson, 1989; Chlif *et al.*, 2007). Higher resistive and elastic works of breathing secondary to the volume reducing, thoracic stiffening, and possibly airway remodelling effects of truncal adiposity (Salome *et al.*, 2008), generate a rapid shallow respiratory pattern both at rest (BMI≥35 kg/m^2) and on exertion (BMI≥30 kg/m2) (Sampson and Grassino, 1983). The increased frequency of breathing in obese people is an adaptive response against the elastic overloading of the chest wall to ameliorate the activity-related respiratory discomfort (Ofir *et al.*, 2007).

Both anthropometric and body compositional measures of adiposity have been consistently shown to be negatively related to FVC and FEV_1 in adults. In a cross-sectional analysis of the British Regional Heart Study, adiposity measures (WHR, WC, FM, and %BF) were inversely related to height-standardised and BMI-adjusted FVC and FEV_1 but not FEV_1/FVC in men aged 40–59 years (Wannamethee, Shaper and Whincup, 2005). The BMI-independent inverse relationship between WC and spirometric parameters was also corroborated by the Humboldt Study that reported 13ml and 11ml decrease in FEV_1 and FVC per 1cm increase in WC (Chen *et al.*, 2007).

In addition to the cross-sectional negative impact of adiposity on pulmonary function, respiratory capacity tends to deteriorate with progressively accumulating total and truncal fat. Sutherland *et al.* demonstrated that BIA-estimated %BF and trunk fat mass (TFM) were inversely associated with spirometric and plethysmographic parameters in non-smoking non-asthmatic young adults (with stronger effect in men) from Dunedin Multidisciplinary Health and Development birth cohort at 32 years (FEV_1, FVC, TLC, FRC and RV) and between 32 to 38 years (FEV_1 and FVC, FEV_1/FVC (women), TLC, FRC and RV(men)), indicating the longitudinal effect of total and central adiposity on static and dynamic measures of lung function (Sutherland *et al.*, 2016). Similarly, in a large prospective study of adults aged 18-72 years, the longitudinal changes in weight, BMI, WC, and %BF over five years were inversely associated with height-adjusted changes in FVC and FEV_1. These associations were also dependent on gender and pre-existing adiposity.

In men, 1 standard deviation (SD) increase in BMI, WC, and %BF was respectively associated with 114, 91, and 54 ml decrease in FVC as well as 78, 66, and 52 ml decrease in FEV_1. These changes were two to three times higher than those recorded in women. In addition, 5-year adiposity change had a significantly larger impact on FVC and FEV_1 in those with a BMI≥25kg/m^2 at baseline as compared to participants who were normal-weight at baseline, particularly among men. FEV_1/FVC ratio remained unchanged despite alterations in the adiposity status of the participants (Fenger *et al.*, 2014). Sex-specific changes in the spirometric indices of the overfat individuals can be due to the differential distribution and function of the adipose tissue, anatomical and physiological dissimilarities of the pulmonary structures, and varied risk profile of men and women (Chen *et al.*, 2012; Karastergiou *et al.*, 2012).

Over time, however, the lung function (FVC, FEV_1) tends to decline with increasing adiposity. Progressive deterioration of pulmonary function in the individuals with excessive adiposity is supported by the CARDIA (Coronary Artery Risk Development in Young Adults) study that estimated 10-year FVC and FEV_1 reductions of 138ml and 47ml in non-smoker and non-asthmatic adults with baseline BMI ≥ 26.4 kg/m^2. This multicentre cohort study revealed that ≥ 6 kg/m^2 gain in baseline BMI of overweight or obese individuals would be respectively associated with 264ml and 216ml decrease in the estimated FVC and FEV_1 over 10 years (Thyagarajan *et al.*, 2008). Likewise, a longitudinal study of older adults found that over a 7-year follow-up, height-adjusted FVC and FEV_1 dropped by 46 ml and 31ml per 1cm increment in sagittal abdominal diameter (SAD) in the elderly Caucasians (Rossi *et al.*, 2008).

Apart from the detrimental mechanical effects of increased adiposity on the static and dynamic lung volumes (King *et al.*, 2005), the unfavourable inflammatory profile and immunometabolism of overfat adults may also worsen their respiratory capacity. In a long-term follow-up of the participants in the CARDIA study, higher serum adiponectin levels at year 15 examination were associated with higher FVC and FEV_1 (but not FEV_1/FVC) at year 20 examination, independent of obesity. Thus, persistently reduced adiponectin levels in centrally obese individuals may restrict their thoracic compliance and narrow peripheral airways. However, this association was no longer significant after adjustments for the homoeostasis model

assessment for estimating insulin resistance (HOMA-IR) and C-reactive protein (CRP), denoting that the adiponectin-lung function association may be mediated via insulin-sensitising and anti-inflammatory actions of adiponectin (Shore, 2008; Thyagarajan *et al.*, 2010). Maintenance of FEV_1/FVC together with concomitant reductions in FVC and FEV_1 indicates that the airflow limitation in overweight and obese adults is due to restrictive abnormalities rather than the airway obstruction (Thyagarajan *et al.*, 2010).

2.3.2 Adiposity and Pulmonary Disease

2.3.2.1 Obstructive sleep apnoea

A large body of evidence supports the link between excessive adiposity and obstructive sleep apnoea (OSA) in both sexes. In the Sleep Heart Health Study (SHHS), longitudinal changes in weight were non-linearly associated with changes in Respiratory Disturbance Index (RDI), demonstrating a floor effect whereby those with a low baseline RDI did not show further reductions in the severity index of sleep-disordered breathing (SDB) after weight loss. In this study, men and women who gained 10kg or more were respectively 5 and 2.5 times more likely to experience large increases in the RDI (>15 events per hour) over a 5-year follow-up compared with the stable-weight individuals. (Newman *et al.*, 2005). An earlier cross-sectional study of the community dwelling adults enrolled in the SHHS exhibited that BMI and neck circumference (NC) were independent predictors of SDB severity. This study found that the likelihood of a high apnoea-hypopnoea index (AHI) increased by 1.6 and 1.5fold per 1 SD increment in BMI and NC, respectively. (Young, Shahar and Nieto, J, 2002). This relationship is curvilinear, with a greater risk of sleep apnoea or hypopnea in subjects at higher levels of BMI.(Newman *et al.*, 2005).

Of note, truncal adiposity is a stronger predictor of moderate to severe OSA(AHI>10) than general adiposity, with ORs of 2.6 and 1.76 being associated with high levels of WHR (>1 in men and >0.85 in women) and NC (>42 cm in men and > 37 cm in women) (Martinez-Rivera *et al.*, 2008). A number of RCTs have also shown beneficial influence of diet-induced weight loss on mild as well as moderate to severe (Johansson *et al.*, 2009; Tuomilehto *et al.*, 2009). Importantly, pharyngeal

fat quantity also correlates directly with the severity of OSA (Shelton *et al.*, 1993). Excessive accumulation of fat around the pharyngeal airway enclosed by maxillomandibular bony structures causes anatomical imbalance in the upper airway (UA) and elevates extraluminal pressure on the upper respiratory tract to the critical point of closure, particularly in the retropalatal (and retroglossal) segments where the susceptible upper airways lacking anatomical support are overwhelmed by the passive intra-pharyngeal pressure and collapse during expiration at sleep (Horner, 2007).

In addition to the adipose tissue surrounding the upper airways, visceral fat area (VFA) has been shown to be a strong correlate of OSA indices (AHI and SaO_2) in obese men independent of their BMI, %BF or subcutaneous fat area (SFA) (Vgontzas *et al.*, 2000). Notably, mid and lower-face fat volume were significantly correlated with NC, subcutaneous adipose tissue (SAT), and (more strongly) visceral adipose tissue (VAT) (Sutherland *et al.*, 2011). It is worth mentioning that visceral adiposity appears to be a better predictor for OSA severity than cervicofacial fatness. In a German study of men with suspected OSA, intraabdominal adipose tissue quantified by nuclear MRI as well as serum leptin levels were significantly correlated with AHI whereas subcutaneous cervical fat and parapharyngeal fat did not show significant correlations (Schäfer *et al.*, 2002).

Finally, dysregulated release of adipokines and pro-inflammatory cytokines from central depots of adipose tissue may deteriorate cyclical neuro-anatomical interactions involved in the feedback control of respiratory system during sleep, destabilising breathing pattern and increasing severity of OSA (Isono, 2009).

Therefore, central and cervical adiposity contribute to the development and worsening of OSA albeit via different mechanisms.

2.3.2.2 Chronic Obstructive Pulmonary Disease

The available data are suggestive of the variable, even paradoxical, effects of obesity on different phenotypes and stages of COPD. In a cross-sectional analysis of the Function, Living, Outcomes, and Work (FLOW) study, the frequency of having a BMI in the obese range was two times higher in patients with early stage COPD

compared with the general population (Eisner *et al.*, 2007). Earlier, the Tucson Epidemiologic Study of Airways Obstructive Diseases (TESAOD) had shown that the risk of chronic bronchitis was highest in patients with BMI≥28 kg/m^2 (OR=1.80; 95% CI:1.32 to 2.46) whereas the odds of being diagnosed with emphysema was highest in those with BMI<18.5 kg/m^2 (OR=2.97; 95% CI: 1.33–6.68). For both phenotypes of COPD, the OR was lowest in the normal weight and mildly overweight patients (Guerra *et al.*, 2002).

Besides the higher prevalence of obesity in subjects with COPD compared to the general population (23% vs 11%), an interaction between obesity and degree of COPD severity was also reported in a Dutch cohort of COPD patients. In this study, the prevalence of obesity was inversely related to the clinical stage of COPD defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (Steuten *et al.*, 2006). However, the population-based PLATINO (Proyecto Latinoamericano de Investigacion en Obstruccio´n Pulmonar) study found a proportionally higher frequency of obesity among subjects without COPD as compared to those with objectively-defined COPD (32% vs 23%) (Montes de Oca *et al.*, 2008). Nevertheless, a recent study of the nationally representative data from the Behavioural Risk Factor Surveillance System (BRFSS) that reported a dose-response relationship between the level of obesity and COPD in lifetime non-smoker white adults. In this study, men and women with obesity class III (BMI≥40 kg/m^2) were respectively 3.2 and 4 times more likely to have COPD as compared to their normal weight counterparts, even after adjustments for age and socioeconomic status (Fuller-Thomson *et al.*, 2018). These inconsistencies may be due to heterogenous study population and designs as well as disparate confounders, comorbidities, and clinical characteristics.

Clinical picture and functional capacity of patients with COPD are concomitantly influenced by their state of adiposity as well. A secondary data analysis of veterans with spirometry-diagnosed COPD indicated that obese subjects had poorer health-related quality of life (measured by the higher total score on the St. George's Respiratory Questionnaire (SGRQ)). Moreover, they had approximately 5-fold higher odds of living with moderate to severe dyspnoea (MRC score ≥ 2) compared with their normal weight counterparts, irrespective of the severity of their airflow obstruction. By contrast, lung function was less impaired in obese veterans than in

the normal weight patients (FEV_1 55% versus 44% of the predicted value). This contradictory finding can be explained in a few ways. Firstly, more severe symptoms and poorer quality of life in obese patients may prompt them to seek medical care at earlier stages of COPD. Excess weight of this group may also be an indicative of their earlier smoking cessation. Lastly, as mentioned above, obesity may be inversely related to more sever clinical phenotypes of COPD (Cecere *et al.*, 2011).

Despite the possibility of receiving care at less advanced stages of the disease, obese patients with COPD suffer from deteriorated physical performance and exercise tolerance. In the FLOW study, 1kg increase in the BIA-estimated fat mass was predictive of 6% and 4% higher risk of self-reported functional limitation as well as 13 and 11meters shorter distance of walking in 6 minutes (6MWD) in men and women, respectively. In addition, total physical performance score of male and female patients dropped respectively by approximately 0.07 and 0.1 score per 1cm increment in SAD (Eisner *et al.*, 2007). In line with these observations, a retrospective chart review of COPD patients undergoing pulmonary rehabilitation displayed that, despite higher FEV_1 %predicted and FEV_1/FVC records, obese outpatients scored significantly lower on the self-reported Chronic Respiratory Questionnaire (CRQ-SR) and Pulmonary Functional Status Scale (PFSS). They also had shorted 6WD and greater fatigue as compared to their non-obese counterparts (Ramachandran *et al.*, 2008).

The abnormal ventilation and greater ventilatory demand of the chronically obstructed lungs (V/Q mismatch, metabolic acidosis, hypoxaemia, hypercapnia, increased sympathetic tone) that arise from reduced elastic recoil, airflow limitation, air-trapping, dynamic hyperinflation and neuromechanical dissociation are aggravated by the excessive fat accumulation in obese patients with COPD.

In addition to the altered mechanics of respiration, the complex interplay of adipose tissue and skeletal muscle dysfunction, adiposity-fuelled and hypoxia-induced systemic and local inflammatory responses as well as overlapping comorbidities should not be overlooked in the setting of COPD (Franssen *et al.*, 2008; Garciá-Rio *et al.*, 2014). On this score, exploratory analysis of data from the multicentre prospective Genetic Epidemiology of COPD (COPDGene) study illuminated a dose-

dependent relationship between obesity class and COPD-related outcomes. Adjusted for age, sex, ethnicity, education, FEV_1/Ht^2, smoking, and comorbidity count, patients with obesity class III (BMI≥40 kg/m^2) whose COPD had been confirmed by spirometry had significantly worse quality of life (QoL) (measured by the St. George's Respiratory Questionnaire (SGRQ) score), lower 6MWD, more severe dyspnoea (measured by the modified Medical Research Council (mMRC) score) and higher odds of moderate and severe acute exacerbation of COPD (AECOPD) compared to patients with other classes of obesity as well as normal-overweight subjects, with the largest differences observed between obese class III and referent groups (BMI 18.5-29.9 kg/m^2).

In contrast to the adverse effect of excessive adiposity on the symptomatology and QoL of COPD patients (Cecere *et al.*, 2011), there are several lines of evidence suggesting an inverse relationship between obesity and mortality in these patients. In a prospective follow-up of the Copenhagen City Heart Study, > 3kg/m^2 BMI loss over 5 years predicted almost 70% and 60% rise in the estimated rate ratios of all-cause mortality in subjects with and without COPD, respectively. Furthermore, more than 3kg/m^2 BMI loss was associated with 2-fold increase in the estimated COPD-related relative mortality rate. In comparison, > 3kg/m^2 gain in BMI did not change the estimated COPD-related death rate. Notably, baseline BMI had a modifying effect on the link between weight change and mortality in severe cases of COPD. While weight gain was a predictor of better survival among patients with BMI<25 kg/m^2, overweight or obese patients would have the lowest mortality rate if their weight remained unchanged (Prescott *et al.*, 2002). Comparably, a Cox regression analysis of data from the Association Nationale pour le Traitement A Domicile de l'Insuffisance Respiratoire chronique (ANTADIR) Observatory, 5-year survival rate and the length of hospital admission among patients with severe COPD receiving long-term oxygen therapy was highest (59%) in obese (BMI ≥ 30 kg/m^2) subjects. In contrast, underweight patients (BMI<20 kg/m^2) had the lowest survival rate (24%) and longest hospitalisation (29.6 ± 40.4 days) (Chailleux, Laaban and Veale, 2003).

The pattern of relationship between BMI and survival rate in COPD patients seems to be affected by the clinical stage of their disease. Whereas patients with $FEV_1 \geq$ 50% of the predicted value demonstrate a U-shaped association with the highest survival being estimated for normal-weight/overweight BMI ranges (RR for all-

cause mortality: 0.96 and 1.24), those with severely impaired ventilatory function (FEV_1<50% of the predicted value) exhibit a linearly negative relationship with highest all-cause and COPD mortality rate estimated for underweight BMI range (RR 1.63 and 2.20) (Landbo *et al.*, 1999).

These observations are in contradistinction to the epidemiological data stressing the harmful effect of obesity on life expectancy in the general population. The pathophysiological mechanisms underlying this "obesity paradox" are still poorly understood but differential effects of body composition phenotypes as well as metabolic alterations and immunoregulatory adaptations may be plausible reasons. This phenomenon was elegantly explored in a multicentre observational study of patients with COPD from the BODE (Body Mass Index, Airway Obstruction, Dyspnoea, Exercise Capacity) cohort registry. After a median follow up of 51 months, BMI demonstrated inverse associations with the BODE index, hyperinflation, and FEV_1/FVC ratio, U-shaped relationships with the mMRC scale and SGRQ score, and an inverted U-shaped relationship with 6MWD. The underweight group (BMI <21kg/m^2) had the shortest Kaplan-Meyer estimated survival time (52 months) whereas the obese group (30 ≤ BMI<35kg/m^2) had the longest survival (120 months), followed by very obese (BMI≥35 kg/m^2) group (114 months). Adjusted for age and obstruction severity, all-cause mortality risk ratio was highest in the underweight (RR:1.57) and lowest in very obese group (RR: 0.65). Interestingly, a proportional hazard analysis of data from the NHANES III elucidated that, adjusted by age, gender, ethnicity, smoking, current oral corticosteroid use, and degree of airway obstruction, patients with the underweight (BMI<18.5 kg/m^2) and extreme obesity (BMI>40 kg/m^2) states had the highest risk of death from respiratory disease (HR:7.10 and 5.78) and chronic lower respiratory disease (excluding asthma) (HR:14.80 and 13.69) compared to patients with other BMI categories. Surprisingly, extremely obese patients did not have a higher all-cause mortality (Jordan and Mann, 2010).

With regard to this obesity paradox in COPD, indicated by the differential clustering of COPD comorbidities and clinical expressions across BMI groups and the aggregation of respiratory-specific mortality at the extremes of BMI spectrum, it can be postulated that depleted lean (and fat) mass as well as excessive adiposity are associated with higher COPD-related morbidity and mortality via distinct

pathophysiological mechanisms. While undernourished individuals have more severe phenotypes and higher risk of short-term death, obese patients with early-stage presentations experience a less aggressive clinical course with more frequent cardiovascular comorbidities and higher risk of long-term death (time differential hypothesis) (Divo *et al.*, 2014). The increased risk of cardiometabolic morbidity and all-cause mortality in obese patients with COPD can be partly attributed to the low-grade chronic systemic inflammatory state and abnormal metabolic profile that prevail in this condition. Systemic inflammation in these patients is reinforced by the concomitant occurrence of metabolic syndrome which has been shown to be more prevalent in subjects with COPD compared with the age- and sex-matched controls (Marquis *et al.*, 2005; Watz *et al.*, 2009).

Fat depots are another source of inflammation in COPD. Overweight/obese patients with COPD (BMI 28.2–44.7 kg/m^2), have higher interleukin (IL)-6, tumour necrosis factor (TNF)- α, CRP, and leptin concentration and lower adiponectin levels compared to normal weight subjects. In this relation, it has been suggested that FM is the main determinant of IL-6 and TNF- α, and CRP levels whereas BMI is the strongest predictor of leptin and adiponectin levels in men undergoing pulmonary rehabilitation for stable COPD (Poulain *et al.*, 2008).

Despite the presence of systemic inflammation in a large proportion of patients with COPD compared with control subjects, it does not differ across stages of disease. Hence, inflammatory responses at the adipose tissue (not the systemic) level may contribute to clinical expression and morbidity burden of COPD. In a prospective cohort study of patients who met ATS/ERS diagnostic criteria for COPD, the expression of hypoxia-inducible proinflammatory signalling molecules, i.e., CD40, MKK4 (mitogen activated protein kinase (MAPK) kinase 4) and JNK (c-Jun NH2-terminal kinase) was significantly higher in the abdominal SAT biopsies of subjects with more advanced disease (GOLD stage IV) and significantly lower BMI, fat mass index (FMI), and fat-free mass index (FFMI) as compared to those with less severe COPD (GOLD stage I-III). In addition, the upregulation of these inflammatory mediators was associated with lower P_aO_2, BMI and adipocyte diameter (Tkacova *et al.*, 2011).

Although the interconnection of adiposity-incited, lung-specific, and systemic inflammation has yet to be proved, the role of chronic hypoxaemia, regional distribution and endocrine function of fat and lean mass and white adipose tissue (WAT) macrophage infiltration in the pathophysiology of systemic inflammation in COPD seem plausible (Rutten, Wouters and Franssen, 2013).

2.3.2.3 Asthma

Obesity is now recognised as a risk factor for asthma in adults and children. A large battery of epidemiologic studies indicate that obese patients have a higher risk of developing asthma.

Progressive rise of asthma risk across the increasing levels of BMI was first shown in the 26-year follow-up of birth cohorts from the British Cohort Study (BCS70). This study indicated that young, particularly female, adults with obesity had the highest odds of suffering from asthma in the previous 12 months compared with non-overweight/obese subjects (OR:1.43; 95% CI (0.82, 2.50) in men; OR:1.84 ; 95% CI (1.19, 2.84) in women) (Shaheen *et al.*, 1999). A meta-analysis of large-scale prospective studies reported a dose-response effect of BMI on the adjusted annual OR of incident asthma. Compared with normal-weight individuals, overweight and obese subjects had respectively 38% and 92% higher chance of being diagnosed with asthma over 1-year follow-up (Beuther and Sutherland, 2007).

In contrast to the U-shaped association of BMI and COPD-related adverse outcome, the relationship between BMI and adult-onset asthma appears to follow a J-shaped pattern. Based on the Finnish Twin Cohort study, the risk of asthma increased by approximately 50% and 60% in the underweight and overweight subset of COPD-free individuals as compared to their normal-weight counterparts. Notably, obesity was associated with 2-fold increase in the incidence of asthma over an 8-year period. During follow-up, multi-covariate adjusted odds of developing asthma was about 40% higher in those who gained more than 10kg compared with subjects whose weight increased less than 10kg (OR:1.41; 95% CI (0.50, 3.98) for men and OR:1.45; 95% CI (0.54, 3.90) for women) (Huovinen, Kaprio and Koskenvuo, 2003).

By contrast, some longitudinal studies have pointed to a reverse association. The Zurich Cohort Study of young adults revealed that the asthmatics were 4 times more likely to become obese over 20 years as compared to those without asthma (OR:3.9; 95% CI (1.2, 12.2)). Also, pre-existing asthma was predictive of higher risk of weight gain (0.15 kg/m^2 per year) and obesity (OR:3.2; 95% CI (1.3, 8.2)) later in life (Hasler *et al.*, 2006).

Notwithstanding these reports, there is substantial evidence that the aggregation of fat mass precedes development or deterioration of asthma in adults. The largest prospective study of adiposity-asthma link which followed Norwegians aged 14–59 years for an average of 21 years found that the adjusted risk of self-reported asthma was significantly higher in men and women who were overweight (RR (95% CI):1.27 (1.13, 1.43) and 1.30(1.17, 1.45), respectively) or obese (RR(95% CI):1.88(1.28, 2.76) in men and 2.21 (1.75, 2.80) in women) as compared to their normal-weight peers. The incidence of asthma increased respectively by 7% and 10% for each unit BMI increment in men and women subjects (Nystad *et al.*, 2004).

Besides BMI, body fat has been shown to be a predictor of asthma incidence. The assessment of birth cohorts from the Dunedin Study indicated that the odds of having asthma increased by 30% per 1SD increment in %BF of women. In addition, adiposity was found to be a contributor to the airflow obstruction. While higher %BF predicted greater airway obstruction in female participants, it was associated with less severe obstruction (higher FEV_1/FVC) in males, particularly among smokers (McLachlan *et al.*, 2007).

The examination of data from the PRIT (Prevalence of Cardiovascular Risks in General Hospital Workers) 2001 survey showed that the likelihood ratio (LR) for asthma symptoms in female (but not male) Hispanic workers rose proportionally with increasing WC from 73.5 cm to 86 cm. WHR was not a predictor of asthmatic symptoms in any of these groups (Del-Rio-Navarro *et al.*, 2003). Sex-dependent association between abdominal obesity and physician-diagnosed asthma was subsequently observed in the cross-sectional Humboldt study where abdominally obese women (WC ≥100 cm) had greater odds of life-time and recent asthma (adjusted OR (95% CI): 1.95 (1.11, 3.43)) than those with WC<100cm. Large WC

did not significantly increase the risk of life-time or recent asthma in men (Chen *et al.*, 2005).

Not only does excessive adiposity increase the risk of adult-onset asthma, but it impairs pulmonary function. Longitudinal exploration of data from the Health2006 and the Health2006 follow-up studies illustrated a sex-dependent inverse relationship between 5-year changes in adiposity measures and parameters of lung function in a general population. In the asthmatic subgroup, 1SD increase in BMI from baseline to follow-up significantly predicted negative changes in FEV_1 (−96.4±16.7ml) and FVC (−109.7±24.4ml) in men. Despite declining trends in women, the contribution of adiposity to the worsening of lung function was not significant. Regardless of asthma status, changes (1SD) in all measures of adiposity (BMI, WC, %BF) were associated with significantly inverse changes in FEV_1 (−78.5, −66.4, and −52.0 ml for men; −25.5, −23.4, and −19.2 for women) and FVC (-113.6, -90.7, and -54.3ml for men; -32.6, -28.1, and -18.0 ml for women) but not FEV_1/FVC ratio. The effect of adiposity on spirometric parameters was more than three times stronger in male participants than females and was not modified by atopy or fractional exhaled nitric oxide (F_eNO) levels (Fenger *et al.*, 2014). In a cross-sectional analysis of NHANES data, BMI, WC, and waist to height ratio (WHtR) were all related to the worsening of lung function (FEV_1, FVC, $FEF_{25-75\%}$) in men and women with asthma, with WHtR being the strongest correlate of all indices in both sexes. Notably, WC and WHtR were significantly correlated with reduced FEV_1/FVC ratio only in males (Sadeghimakki and McCarthy, 2019).

In addition to pulmonary function, symptom burden, airway hyperresponsive (AHR), inflammation, and treatment response in patients with asthma are also influenced by their adiposity status. The normative aging study provided the earliest evidence on the relationship between obesity and AHR in asthmatic men. In this prospective cohort study, there was a U-shaped association between initial BMI and the risk of incident methacholine airway hyperresponsiveness, with the odds of a positive methacholine challenge test being 7.5fold greater in veterans who had the lowest (≤24.3 kg/m^2) or highest(>29.4 kg/m^2) baseline BMI as compared to other patients (Multivariable OR (95% CI): 7.5 (1.3, 44.7) and 7.5 (1.5, 37.8), respectively). Additionally, annual changes in BMI were linearly related to the odds of developing AHR over 4 years. Whereas 0.4-1.9 kg/m^2 increase in BMI per year

predicted 55% higher risk of AHR, losing 0.2-1.5 kg/m^2 per year decreased the 4-year risk of AHR by 32%. Irrespective of methacholine challenge, no significant difference in percentage predicted values of FEV_1 or FVC was observed across quintiles of BMI (Litonjua *et al.*, 2002).

In a recent prospective evaluation of severely obese patients with mild-moderate asthma who had undergone laparoscopic adjustable gastric banding (LAGB), surgically induced persistent weight loss (14.8±3.2 kg/m^2) at 5-year follow-up was associated with significantly improved lung function (percentage predicted values of FEV_1 and FVC), asthma control (Asthma Control Test (ACT) total score), and health related QoL (the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) score). In comparison, these outcomes remained unchanged in the control group from baseline to 5-year follow-up (Maniscalco *et al.*, 2017).

Likewise, a longitudinal study of morbidly obese (BMI>40 kg/m^2) with physiologic evidence of asthma (determined by methacholine challenge or bronchodilator response) who underwent bariatric surgery showed significant improvements in spirometric indices (percentage predicted values of FEV_1 and FVC), asthma control (lower scores on the Juniper Asthma Control Questionnaire (ACQ); less frequent use of short-acting β-agonists (SABA)), quality of life (Asthma Quality of Life Questionnaire (AQLQ) score), AHR (increased Methacholine PC20 estimates) at 12-month follow-up. Importantly, clinical phenotype of asthma affected changes in several endpoint measures subsequent to bariatric surgery. AHR improved only in patients with normal IgE level (non-atopic patients). In spite of favourable changes in symptom severity and asthma control, markers of allergic inflammation (airway eosinophil count) did not increase postoperatively (Dixon, Pratley, *et al.*, 2011).

It should be emphasised that asthma is a heterogenous multifactorial disease with a multitude of clinical characteristics. The landmark Severe Asthma Research Program (SARP) identified 5 distinct phenotypes of asthma using agglomerative discriminant cluster analysis of demographic, pathobiologic, and clinical data from non-smoking asthmatics. Remarkably, obesity-asthma association was more recognisable in cluster 3 phenotype characterised by late-onset, female predominance, highest BMI, higher rate of hypertension, low F_eNO and IgE concentration, high sputum neutrophil count, short duration of asthma, less

likelihood of atopy/allergy, mild airflow obstruction, AHR, disproportionate relation of symptoms to pulmonary function impairment, moderate severity, more reliance on medications, and frequent exacerbations requiring oral corticosteroid use (Moore *et al.*, 2010). In this regard, the eosinophilic airway inflammation, assessed directly by quantifying eosinophil counts in induced sputum or indirectly by F_eNO has not been found to be associated with adiposity in asthmatic obese patients (McLachlan *et al.*, 2007).

Contrary to the early-onset allergic asthma (clusters 1,2, and 4 with an increasing order of severity) that involves Th_2-mediated lymphocytic inflammation and airway eosinophilia, mucus hypersecretion, and remodelling (Wenzel, 2012), the inflammatory responses in the adult-onset nonallergic obesity-related asthma (cluster 3) are predominantly mediated by Th_1 cells (Sideleva and Dixon, 2014). This clustered phenotyping may help explain discrepant reports on the temporal relationship of obesity and asthma, sex differences in the adiposity-asthma associations, inconsistent effects of BMI and weight change on the AHR, and varied responses of asthma outcomes to the adiposity measures in children and adults. A large majority of these studies did not differentiate between early-onset Th_2 allergic asthma and late-onset non-Th_2 nonallergic asthma when explored the possible associations between adiposity and asthma endpoints.

Excessive adiposity can be linked to the worsening of asthma-related outcomes via several potential mechanisms. From a mechanical perspective, the accumulation of truncal fat restricts lung capacity (TLC, FRC), diminishes ERV, and reduces lung compliance, leading to tidal-volume breathing, EFL, air-trapping, peripheral airway damage and ventilation/perfusion mismatch (Salome, King and Berend, 2010). Moreover, obese people have been shown to have more reactive airways due to their overstretched smooth muscles and reduced calibre (Dixon *et al.*, 2010). Bronchial hyperresponsiveness (BHR) or impaired bronchodilation appear to be synergistically augmented by the co-existence of asthma and obesity (Boulet *et al.*, 2005). Further, obesity is associated with inflammatory changes in the airways, including lower eosinophil and higher neutrophil count, Th_1-polarised immune responses, IL-17 related inflammation, and enhanced oxidative responses (Baffi, Winnica and Holguin, 2015).

Concomitant metabolic dysregulation also plays a role in the pathogenesis of obesity-asthma phenotype. Higher levels of plasma and airway leptin, lower L-arginine/asymmetric dimethyl arginine (ADMA) ratio and aggravated oxidative stress may all contribute to the impaired lung function in obese asthmatics (Baffi, Winnica and Holguin, 2015). The imbalance between L-arginine, a precursor of nitric oxide (NO) and a substrate for inducible NO synthase (iNOS) and the ADMA, an inhibitor of NOS, results in the iNOS uncoupling, decreased bronchoalveolar NO bioavailability and impaired bronchodilatory response. This may lead to the worsening of pulmonary function, symptoms, and quality of life in overfat adults with asthma (Holguin *et al.*, 2013). Apart from leptin, increased TNF-α may contribute to the AHR via TNFR-2 signalling that activates the expression of IL17-A, endothelin 1, and trk β, elements crucially involved in the innate airway responsiveness.(Williams *et al.*, 2013).

Along with the excessive fatness, insulin resistance (IR) is thought to be another culprit for the impaired pulmonary function in obese asthmatics. Recently, an investigation of NHANES data showed that IR strengthened the association of obesity and current asthma in adults by 2-fold, although the contribution of IR to the association between visceral adiposity and PFT values was not explored in this study (Cardet *et al.*, 2016). In accord with this finding, a quantitative analysis of the NHANES 2009-2012 data elucidated that the absolute spirometric indices (FVC and FEV_1) were negatively affected by IR in adults with asthma. In this study, IR modified the effect of central obesity (measured by WHtR) on and FVC and FEV_1 so that higher WHtR was associated with impaired lung function only in asthmatics who were insulin resistant (Sadeghimakki and McCarthy, 2019).

IR and the consequent hyperinsulinemia can influence the lung function via several mechanisms. IGF-1 triggers airway smooth muscle proliferation and contractility (Dekkers *et al.*, 2009). Insulin is a promoter of airway smooth muscle contraction and remodelling and a modulator of inflammatory reactions in the lung, especially in asthmatics with metabolic syndrome (Singh *et al.*, 2013). Furthermore, it has been suggested that high insulin levels may alter the diameter of small airways via central neuro-hormonal mechanisms as well (MacIver, Michalek and Rathmell, 2013). The interplay between asthma and IR in centrally obese individuals could also be explained immunologically by the altered activation patterns of monocytes and T

helper cells (Dixon, Johnson, *et al.*, 2011), leading to the predominance of Th_1 and M1 adipose tissue macrophages (Lumeng and Saltiel, 2011; Gerriets and MacIver, 2014).

2.3.3 Lean mass and lung function

As opposed to the deteriorating impact of excess fat on respiratory health and function, well-developed lean mass appears to improve lung physiology and protect against pulmonary dysfunction. Lean mass acts as a link between physical performance and lung function as it is related to respiratory muscle strength (Nishimura *et al.*, 1995). Adjusted for by body fat, fat-free mass (FFM) and muscle strength have been shown to correlate significantly with lung volume and ventilatory capacity among healthy men and women(Enright *et al.*, 1994; Lazarus *et al.*, 1998). DXA-quantified total and segmental muscle mass are directly correlated with spirometric parameters (FVC, FEV_1, $FEF_{25\%–75\%}$) in male and female Caucasians. Among lean mass components, leg and trunk lean mass have been shown to be the strongest age and BMI-matched determinants of FEV_1 and FVC in men and women, respectively (Martín Holguera *et al.*, 2017). Moreover, FFM-depleted individuals exhibit lower respiratory (assessed by maximal inspiratory and expiratory mouth pressures) and peripheral muscle strength (measured by handgrip dynamometry) (Schols *et al.*, 2003) even with a normal body weight (Schols *et al.*, 1993).

The inclusion of muscle mass or FFM components in the reference prediction equations for lung function, improves their accuracy (Cotes *et al.*, 1979; Mengesha and Mekonnen, 1985). For instance, the inclusion of bone-free lean mass (BF-LM) and BMC in the regression models improved the performance of these models in predicting spirometric parameters (FVC, FEV_1, and PEF) as compared to the regression equations simply derived from age and height (Mohamed *et al.*, 2002).

The elevated FFMI augments IC while it diminishes ERV and FRC in both sexes. Because of the sex-specific association of FFM with IC, the effect of leanness on TLC, FVC and FEV_1 is more prominent in healthy men than women (Cotes, Chinn and Reed, 2001). However, one should not forget the opposite effects of FM and FFM on the lung function. These body compartments may cancel out each other's impact on spirometric parameters if not included as distinct variables in the

predictive models, giving the false impression that body size is not a significant covariate of lung function. This may be one of the reasons for the inconsistencies surrounding BMI-lung function associations

Body composition might also modify the association between age and lung function. As men and women grow old, they tend to become physically less active, gain (visceral) adipose tissue and lose skeletal muscle, both contributing to the age-related decline in pulmonary function (Hazzard *et al.*, 2003) due to reduced elastic recoil, chest wall compliance and respiratory muscle function(Enright *et al.*, 1994; Watsford, Murphy and Pine, 2007).The positive association between FFM (and muscle strength) and spirometric indices (FEV_1, FVC, and FEV_1/FVC) has been observed in the elderly men and women both cross-sectionally (Wannamethee, Shaper and Whincup, 2005; Karacan *et al.*, 2008) and longitudinally (Burchfiel *et al.*, 1997). Of note, a longitudinal study of older Italians showed that controlling for baseline lung function, smoking, renal function and sex, FVC diminished by 38ml (95% CI (17, 60)) per 1kg decline in DXA-measured FFM over 7 years. More precisely, individuals with increased SAD and decreased FFM had the highest probability of FEV_1 and FVC decline. In comparison, those with stable FFM and decreased SAD had the lowest frequency of diminished FEV_1 and FVC , denoting the additive effect of excess fat and FFM depletion on lung function impairment in the setting of sarcopenic obesity (Rossi *et al.*, 2008). In addition to the loss of muscle mass, the decline in muscle function (partially caused by intermuscular fat infiltration) may impair respiratory performance in older adults with sarcopenic obesity (Rossi *et al.*, 2011). In this regard, an analysis of the Korean National Health and Nutrition Examination Survey (KNHANES) indicated that pulmonary function was most severely affected in COPD-free older adults who had concomitant low muscle mass and obesity (Moon, Kong and Kim, 2015).

FFM, particularly SMM, is also a significant determinant of the exercise tolerance, clinical course and the prognosis of patients with pulmonary diseases. The prevalence of sarcopenia, defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as low muscle mass plus low muscle strength and/or low physical performance (Cruz-Jentoft *et al.*, 2010), is higher in patients with COPD than COPD-free individuals. In addition, frequency of sarcopenia is higher in the

patients with more advanced COPD as compared to those at earlier stages of the disease (Shimokata *et al.*, 2018).

COPD patients with reduced muscle quantity, quality or strength tend to be older, and at higher risk of cardiovascular comorbidities. The degree of airflow limitation, the intensity of symptoms, the frequency of exacerbations, the level of physical disability and impaired quality of life, as well as the severity of disease are more pronounced in sarcopenic patients with COPD compared to non-sarcopenic patients, especially among men (Jones *et al.*, 2015). Patients with moderate-severe COPD are 3 times more likely to have low FFMI (OR:3.5; 95% CI (2.33, 5.27)) compared to ever-smokers without COPD, independent of their sex or age (Grydeland *et al.*, 2012). FFMI declines progressively with the worsening of COPD, with subjects suffering from GOLD stage 4 disease having the highest prevalence of skeletal muscle mass depletion (Vestbo *et al.*, 2006).

Apart from the established detrimental effect of low BMI on the outcome measures of COPD in different age groups (Landbo *et al.*, 1999; Corrada *et al.*, 2006; Thinggaard *et al.*, 2010), it has been shown that skeletal muscle mass (SMM) depletion, assessed by mid-thigh muscle cross sectional area ($MTCSA_{CT}$) and mid-arm muscle area (MAMA), is a stronger predictor of mortality than BMI in those with severe COPD (Marquis *et al.*, 2002; Soler-Cataluña *et al.*, 2005). Akin to these observations, a recent study of community-dwelling older Taiwanese with objectively diagnosed stable COPD indicated that low (<30 cm) calf circumference (CC) and low (<23.5 cm) mid upper arm circumference (MUAC) were more effective independent predictors of 3-year multivariate mortality (HR (95% CI): 4.40 (1.82, 10.63) and 3.09 (1.30, 7.38), respectively) than low BMI (<21 kg/m^2)(HR (95% CI): 2.78 (1.10, 7.10)) (Ho *et al.*, 2016).

As the lung function deteriorates, the impact of FFM depletion and skeletal muscle deconditioning on the physical disability of the patients also becomes more prominent. In the advanced course of COPD, there is universal loss of body mass (FM and FFM) and muscle wasting. In this context, it appears that depleted lean mass is the strongest correlate of ventilatory disturbance, with FFMI being the most important prognostic factor in moderate-severe COPD (Slinde *et al.*, 2005).

Although muscle depletion may be the consequence of a more severe phenotype of COPD associated with heavy smoking, it could also be a causative factor. Recent data from the population-based BOLD (Burden of Obstructive Lung Disease) study indicated that thin (BMI<20 kg/m^2) male and female never-smokers had higher risk of experiencing moderate-severe COPD (GOLD stage 2 and above) (OR (95% CI): 13.39 (3.67, 48.84) and 2.56 (1.40, 4.71) than their normal-weight counterparts (Lamprecht *et al.*, 2011). Over time, however, the slope of FFM decline in patients with COPD approximates that of controls irrespective of the smoking status. The Health ABC Study revealed striking similarities in multivariate adjusted 7-year trajectories of lean mass, BMC, and quadriceps strength between older adults with mild-moderate obstructive lung disease and smokers as well as never-smokers with normally functioning lungs (Van Den Borst *et al.*, 2011).

Besides depleted SMM, peripheral muscular weakness (measured by quadriceps maximal voluntary contraction force (QMVC)) is also associated with poor survival in patients with moderate-severe COPD (Swallow *et al.*, 2007). In agreement with this finding, a posteriori analysis of the multicentre Phenotype and Course of COPD (PAC-COPD) study demonstrated that after adjustment for ADO (age, dyspnoea, obstruction) index (Puhan *et al.*, 2009). BMI, handgrip strength below 10th centile of the healthy population predicted increased mortality in patients with stable COPD (HR:1.53; 95% CI (1.07, 2.12)) (Burtin *et al.*, 2016).

In patients with COPD, upper and/or lower limb muscular strength not only predict the quantity of life, but they also affect the quality of life. Based on the prospective analysis of data from the multicentre ICE-COLD ERIC (International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts) study, 2-year mortality decreased by 42% and 16% per 5 more repetitions of the 1-minute sit-to-stand (STS) and per 5kg rise in the isometric grip force. Additionally, 1-min STS as a measure of exercise capacity was found to be a strong predictor of 2-year survival with a discriminatory power close to ADO and BODE (BMI, airflow obstruction, dyspnoea, exercise capacity) indices (Muggensturm *et al.*, 2013). It should also be noted that, until advanced stages, COPD patients lose disproportionately higher amount of muscle in lower limbs as they work the upper body muscles more frequently and more extensively, leading to quadriceps atrophy and weakness (Bernard *et al.*, 1998).

Several factors contribute to the loss of lean mass and muscular dysfunction in patients with COPD, including muscle disuse, long-term use of oral corticosteroids, chronic hypoxia as well as systemic and local inflammatory responses. Depending on the severity of pulmonary damage, several myopathological adaptations occur in the skeletal muscles of COPD patients. These include progressive reduction in skeletal muscle capillarisation (due in part to the hypoxia-attenuated VEGF expression) which is related to the degree of airflow obstruction and exercise capacity, fibre type shifting towards an easily fatigable glycolytic profile (due to the impaired muscle oxygen supply) related to BMI and oxidative capacity, (Eliason *et al.*, 2010) and dysregulation of skeletal muscle protein metabolism (caused by disturbances in ubiquitin–proteasome and myogenetic pathways) that leads to muscle atrophy and defective compensatory hypertrophy (Joanisse *et al.*, 2007).

Besides their discrete effects on the health status, functioning capacity, and survival, high FM and low FFM also exert compound impacts on COPD-related outcomes. The new approach toward the assessment of body composition in COPD sufferers is to classify the patients into distinct phenotypes, i.e., normal body composition, obesity, sarcopenia, and sarcopenic obesity (SO). Data from ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study shows that COPD patients with SO have significantly lower physical performance (-28min 6MWD; 95% CI (-45.6, -10.4) and more intense inflammation (1.6 time greater odds of having more than 2 inflammatory markers, 95% CI (1.1, 2.5)) compared to those with normal body composition (Joppa *et al.*, 2016). Across body composition phenotypes, FEV_1, physical functioning (expressed as the quadriceps strength per kilogram ASM) and cycle endurance time have been found to be lower in the sarcopenic patients with COPD as compared to SO (Van De Bool *et al.*, 2015). Better physical performance of the latter group may be secondary to the reduced lung volume that attenuates the static and dynamic hyperinflation in their lungs (Wadell *et al.*, 2011). Static lung hyperinflation (presenting as low IC) has emerged as a risk factor for disease-specific and all-cause mortality in COPD patients (Tantucci *et al.*, 2008). It is, therefore, conceivable that lower lung volumes and larger IC and IC/TLC in COPD patients with higher body weight may improve their ventilatory function (Casanova *et al.*, 2005). This protection is, however, outdone by the increased cumulative risk of morbidity and mortality in patients with sarcopenic

obesity. In COPD patients with SO, depleted SMM, contractile insufficiency, metabolic impairment and myokine dysregulation act in synergy with excessive adiposity to aggravate their adverse outcomes, including insulin resistance, weakened antioxidant capacity, fatigue, fractures, and impaired ventilation as well as the greater risk of dyslipidaemia, metabolic syndrome, type 2 diabetes and cardiovascular disease (Biolo, Cederholm and Muscaritoli, 2014). Thus, it is prudent to include detailed body composition analysis in the risk estimation and multidisciplinary care of patients with chronic pulmonary disease.

In the setting of asthma, recent findings suggest that lean mass may be a better indicator of pulmonary function than fat mass. In the multivariable analyses of data from the year 20 examination of the CARDIA cohort, all indices of fat and lean mass were significantly associated with the adjusted odds for current asthma in females with intermittent or mild-moderate asthma. On the contrary, none of these indices showed significant association with the risk of asthma in male participants except for lean arm muscle index. Moreover, there was a sexual dimorphism for asthma-lean mass association, such that highest tertile of total and regional lean mass indices reduced the risk of current asthma in men but increased it in women (Beckett *et al.*, 2010), providing further evidence to the importance of exploring asthma and its covariates as phenotypic clusters. This observation can be explained by the fact that lean mass is not entirely formed of fat-free tissues, particularly in women whose DXA-measured lean mass is not an absolute measure of the skeletal muscle mass (Sutherland *et al.*, 2008). The marbling of muscles is also a prominent finding in females, a phenomenon which does not depend on their overall fat mass (Miljkovic-gacic *et al.*, 2008). Divergent effects of sex-hormones, adipokines (leptin and adiponectin), and other endocrine products may also be involved (Sood, 2011). Among female cohorts of the CARDIA study, DXA-assessed total lean mass was a stronger predictor of current asthma (OR (95% CI): 1.87 (1.04, 3.36)) than total fat mass (1.46 (0.77–2.77)). Importantly, the association of fat mass and asthma became nonsignificant after the addition of lean mass to the model, indicating the independent effect of lean mass on the asthma risk. Among regional components of lean mass, trunk (OR (95% CI): 2.81 (1.39, 5.69)) and leg (OR (95% CI): 0.40 (0.19, 0.84)) mass indices remained significant predictors of current asthma after adjustment for regional fat components (Beckett *et al.*, 2010). Interestingly, the ORs

for truncal and leg lean mass were directed oppositely, signifying the site-specific metabolic and inflammatory effects of lean tissues (Pelt and Schechtman, 2002; Olsen *et al.*, 2005). At the same time, the possible contributory role of the ectopic fat deposits in the asthma-leanness relationship cannot be ruled out (Berry *et al.*, 2006). It is noteworthy that women have higher physiological (subcutaneous) and (metabolically more active and strongly pro-inflammatory) ectopic fat content (including fat infiltrates in the skeletal muscle) (Kyung-Mook *et al.*, 2011; Sood, 2011). Despite quantitatively lower visceral fat, metabolic activity of this adipose depot is greater in women (Leenen *et al.*, 1992; Rattarasarn, Leelawattana and Soonthornpun, 2004). By contrast, their total and regional lean mass are lower and contain higher intramyocellular triglycerides (Battezzati *et al.*, 2001).

Lean and fat mass exert similarly directed effects on pulmonary function in female subjects with asthma. In a study of non-smoking overweight or obese Australians with objectively diagnosed stable asthma awaiting weight loss intervention, DXA-measured total and regional lean mass correlated negatively with the static (TLC, FRC, ERV) and dynamic lung function (FVC, FEV_1, FEV_1/FVC) parameters in women as were the overall and regional fat mass. Intriguingly, significant relationships were found only between lean and fat mass of the arms with FVC, total and arm lean mass as well as android, thoracic, and arm fat mass with ERV, and arm lean mass with TLC and FRC. In contrast, components of lean mass in men were positively related to static and dynamic lung function whilst their corresponding fat components were negative correlates of these parameters. In male subjects, significant correlations were detected only between android and arm lean mass with TLC and FRC, total lean mass with TLC, and android lean mass with ERV. Nonetheless, total and upper body (android, thoracic, and arm) fat mass in males were positively correlated with leptin levels. Fat content of the arms correlated significantly with the eosinophil count while leg lean mass was the only significant correlate of the systemic inflammation (CRP). In females, however, significant relationships were found between gynoid fat mass with eosinophilic airway inflammation (sputum eosinophil%) as well as lower body (gynoid and leg) lean mass with neutrophilic airway inflammation (sputum neutrophil% and count). In addition, static (ERV) and dynamic (FEV_1/FVC) lung function were oppositely associated with android lean mass in men whilst lean and fat mass were inversely

associated with ERV in women (Scott *et al.*, 2012). These findings suggest sexually dimorphic interplay between body composition, systemic and airway inflammation and pulmonary function in asthmatics, giving substance to the notion that the pathophysiology of asthma varies across clusters of disease.

Cystic fibrosis (CF) is also closely related to the alterations in lean body mass. Adult patients with stable CF have significantly lower total FFM, BMC and regional FFMI than their age or sex matched healthy peers, with regional FFM loss following a hierarchical pattern (greatest FFMI deficit being detected in leg followed by arm and trunk). Furthermore, the magnitude of FFM and BMC loss in all segments is accentuated by the increasing severity of disease (Bolton *et al.*, 2003). Loss of muscle mass and bone organic matrix are thought to be caused by the reduced physical activity and catabolic intermediary metabolism secondary to sustained inflammatory response to chronic pulmonary infection (Ionescu *et al.*, 2002). FFM depletion is also a poor prognostic factor in patients with cystic fibrosis as it underlies reduced inspiratory muscle dysfunction and diaphragmatic thinness. Patients with the loss of DXA-measured FFM ($<5^{th}$ percentile of the reference population) had significantly lower static (VC and TLC) and dynamic (FEV_1% predicted) lung function, (Enright *et al.*, 2007). These important contributions may remain undetected in earlier stages of disease if only body mass and weight are relied upon for the nutritional evaluation of patients, partially explaining why nutritional support fails to improve the health status and pulmonary function of CF patients in spite of inducing weight gain (Thomson *et al.*, 1995). Using serum creatinine as a biomarker of lean muscle mass, a study of adults patients with stable CF from the UK Cystic Fibrosis Registry found that FEV_1 and FVC would increase respectively by 171 ml (95% CI (116, 227)) and 99ml (95% CI (41, 157) in males and by 90 ml (95%CI (46, 133) and 64ml (95%CI (19, 110)) in females per 1SD increment in serum creatine level in the mutually adjusted models. Additionally, compared to patients with normal BMI, those with BMI< 20 kg/m^2 had significantly lower FEV_1 and FVC, whereas overweight/obese (BMI$\geq$25 kg/m^2) men and women exhibited significantly higher FEV_1 and FVC, a trend opposite to that seen in healthy population (Forrester *et al.*, 2013). These observations underscore the crucial role of body composition assessment in the management CF patients.

2.4 Body Composition and Systemic Blood Pressure

2.4.1 Fatness and blood pressure

The ascending trend in the obesity epidemic over the past 20 years has been paralleled by an upward shift in the prevalence of hypertension (Forouzanfar *et al.*, 2016). Obesity, mainly in the form of central adiposity, is a precursor for primary hypertension. In the Framingham study, hypertension was twice as common in obese men and women as normal weight individuals, with those in the highest BMI quartile having higher systolic (SBP) (16mmHg) and diastolic (DBP) (4mmHg) blood pressure than persons in the lowest quartile (Hubert *et al.*, 1983). Likewise, in the second Nurses' Health Study, the 14-year risk of incident hypertension was more than 2 and 4 times higher in young (27-44 years old) overweight and obese women with normal baseline SBP and DBP (multivariable HR (95% CI) : 2.56 (2.43, 2.7) and 4.70(4.45, 4.96), respectively) as compared to their age-matched leaner counterparts (BMI<23 kg/m^2) (Forman, Stampfer and Curhan, 2009). Among the modifiable risk factors (physical inactivity, low DASH score, alcohol consumption, and BMI), BMI was the strongest predictor of hypertension incidence in this population, with an estimated 40% attributable risk for overweight or obese status. Surprisingly, adherence to other low risk behaviours (daily vigorous exercise, high DASH score, low alcohol intake, and minimal use of non-narcotic analgesics) did not reduce the HR of incident hypertension in obese women, implying the significantly role of weight loss in primary or secondary prevention of elevated systemic blood pressure. The efficacy of weight-loss as a part of lifestyle modification in the control of hypertension has been established by several studies. The results of the multicentre Trials of Hypertension Prevention (TOHP) Phase II showed that both SBP and DBP decrease significantly at 6 (3.7 mmHg SBP; -2.7 mmHg DBP), 18 (-1.8mmHg SBP; -1.3mmHg DBP), and 36 months (-1.3mmHg SBP; -0.9mmHg DBP) in overweight or obese individuals (30 to 54 years old) with above-normal nonmedicated blood pressure (BP) who underwent weight-loss dietary interventions as compared to the control group. In particular, the relative risk (RR) of hypertension at 36-month follow-up was significantly lower in those who successfully maintained their lost weight (at least 4.5 kg) as compared to the relapse and no-loss group (RR (95% CI): 0.46(0.25, 0.84) and 0.31(0.18, 0.55), respectively) (Stevens *et al.*, 2001). It should be noted, however, that the association

of adipose tissue with arterial pressure varies by ethnicity and fat distribution. Nevertheless, visceral adiposity has been shown to be consistently related to the rise in blood pressure. The multidetector CT sub-study of the Framingham Heart Study Offspring and Third-Generation Study cohorts revealed that in the multivariable adjusted models, VAT was a more powerful predictor of SBP and DBP than SAT in both men and women. The association between VAT and arterial pressure remained significant after adjustment for BMI and WC (Brion *et al.*, 2007). Findings from the IRAS (Insulin Resistance and Atherosclerosis) family study also indicated that the odds of being hypertensive was significantly higher in Hispanic and African American adults in the highest tertiles of both VAT and BMI (OR:6.30 and OR:3.50, respectively) compared with those in the lowest collective tertile (Foy *et al.*, 2008). BP-raising effect of greater central adiposity was corroborated by the Ohtori Study which demonstrated 5-fold increase in the risk of high-normal pressure or hypertension among Japanese men in the highest tertile of intra-abdominal fat area (IAFA) as compared to those in the lowest tertile, controlling for multiple confounders including abdominal subcutaneous fat area (ASFA), total subcutaneous fat area (TSFA), and insulin resistance. In the multivariate models, none of these measures were significant predictors of the outcome (Koh *et al.*, 2011).

Adipose tissue interacts with the cardiovascular system through haemodynamic, neurohumoral, and renal mechanisms (Hall *et al.*, 1993). Compared with lean people, obese subjects have higher arterial pressure, heart rate, glomerular filtration rate (GFR), renal sodium reabsorption, renal and muscular sympathetic activity and perfusion (in the uncomplicated ABCD), as well as plasma insulin levels. Moreover, the incidence of (eccentric and concentric) left ventricular hypertrophy (LVH) is higher in obese individuals. By contrast, baroreflex sensitivity, cardiac diastolic function, muscle blood flow reserve, cardiac sympathetic activity and insulin sensitivity tend to be lower in the subjects with overfatness (Hall *et al.*, 2015). These abnormal changes in vasculature are due, in part, to endothelial dysfunction, vascular stiffening and atherosclerosis stemming from adiposity-related inflammation, oxidative stress, neurohumoral overactivity, hyperglycaemia, and lipotoxicity (Lyon, Law and Hsueh, 2003; Wildman *et al.*, 2003). Central obesity has also deleterious effects on renal pressure natriuresis. The accumulation of WAT in visceral, retroperitoneal and perinephric areas compresses the kidneys, rising

intrarenal and subsequently systemic arterial pressure. Retroperitoneal and renal sinus fat deposition may also induce inflammation and interstitial oedema in the extracellular matrix of renal medulla, compressing the loops of Henle and vasa recta, and secondarily decreasing medullary and tubular perfusion which serves as the stimulus for increased renal sodium reabsorption (Hall, Brands and Henegar, 1999; Hall *et al.*, 2014). Additionally, ectopic intrarenal fat may induce kidney damage through mitochondrial dysfunction and endoplasmic reticulum stress (Unger *et al.*, 2013). The other factor involved in the association between adiposity-induced renal injury and hypertension is the local and systemic activation of renin angiotensin aldosterone system (RAAS).This escalates renal Na reabsorption, constriction of efferent glomerular arterioles, and intraglomerular hydrostatic pressure, deteriorating harmful interplay of kidney dysfunction and hypertension (Hall *et al.*, 2012; Landsberg *et al.*, 2013). The activation of sympathetic nervous system (SNS), particularly renal sympathetic nerve activity (RSNA) is the third important mechanism mediating BP-raising effect of visceral adiposity. It stimulates RAAS and renal sodium reabsorption as well vascular tone (Lohmeier and Iliescu, 2013). Other factors contributing to SNS activation in the setting of obesity-induced hypertension include baroreflex dysfunction, OSA-triggered chemoreceptor reflexes, hyperinsulinemia, and increased angiotensin II.

Recent findings also stress the pivotal role of central leptin-melanocortin pathways in the pathophysiology of adiposity-related hypertension. In this respect, chronic hyperleptinemia activates the CNS proopiomelanocortin (POMC)- melanocortin 4 receptor (MC4R) system via Janus tyrosine kinase 2 (JAK2)- signal transducer and activator of transcription 3 (STAT3), insulin receptor substrate 2 (IRS2)-phosphatidylinositol 3-kinase (PI3-K), and Src homology-2 tyrosine phosphatase (SHP2) mitogen-activated protein kinase (MAPK) which in turn stimulates vasomotor centres in the brain stem and spinal sympathetic preganglionic neurons, leading to increased SNS, RNSA, and BP. This hypertensive effect of central adiposity is amplified by the concurrent endothelial dysfunction and selective resistance to anorexigenic and weight-reducing actions of leptin (Hall et al., 2015). Thus, visceral adiposity may initiate and promote essential hypertension by inducing metabolic dysregulation, kidney injury, and Na retention.

2.4.2 Leanness and blood pressure

Unlike the clear relationship between adiposity and BP, findings on hypertension-leanness association have been inconsistent. A study of non-underweight young men reported a J-shaped relationship between DXA-measured lean mass percentage and submaximal SBP recorded during graded exercise test, with men in 2nd to 4th quintiles having significantly lower submaximal SBP at various intensities of exercise than those in the lowest and highest quintiles (Prasad *et al.*, 2016). In the Tobago Health Study, baseline and 6-year decrease in calf muscle attenuation (as an indication of intramuscular fat infiltration) determined by peripheral quantitative CT (pQCT) were significant predictors of newly developed hypertension among black men even after adjustment for BMI or WC and intermuscular adipose tissue (IMAT). This underscores the contribution of intramuscular adiposity to BP rise, possibly via adiposity induced RAAS activation and impaired intramuscular insulin action (Zhao *et al.*, 2017). In contrast, BIA-derived MAMC and LBM were positively associated with SBP in Turkish university students (Vaziri *et al.*, 2015). In a cohort study of postmenopausal women, DXA-measured total and regional (trunk, arm and appendicular but not leg) lean mass indices (LMI) were positively correlated with SBP and DBP, independent of age, physical activity, and total FM. Nonetheless, most of these indices lost their significance after adjustment for WC, except arm LMI. Interestingly, all lean mass indices showed significantly positive relationship with anthropometric and DXA-derived measures of fatness. There was a significant interaction between arm LMI and WC such that metabolic syndrome was more prevalent in women who had larger waist and higher arm LMI as compared to other combinations of WC and arm LMI (Peppa *et al.*, 2014), suggesting that lean mass may potentially link central adiposity to cardiometabolic health in this subpopulation. Analogous to these observations, a large study of community-dwelling Chinese adults found higher multivariable (including fat mass) adjusted risks of prehypertension and hypertension in subjects with increased total skeletal muscle index (SMI) measured by DXA (OR (95%CI): 1.34 (1.16,1.54) and 1.55 (1.35,1.78), respectively). The android to gynoid fat ratio (AOI) as an indicator of central obesity was a very strong predictor in these models (OR (95%CI): 5.86 (2.72,12.62) and 12.05 (5.74,25.31), respectively). Notably, high arm but not leg LBM was the significant predictor of elevated SBP and DBP, pointing to the BP-

rising potential of upper-limb muscularity (Ye, 2018). One possible explanation for these findings can be LVH, carotid wall thickening, arterial stiffness (Leischik *et al.*, 2014; Moreno *et al.*, 2015), myofiber type shift in hypertrophied muscles (DiCesare *et al.*, 2017), and SNS activation (Fossum *et al.*, 2004; Saito, Iwase and Hachiya, 2009) in (obese or intensively exercising) individuals with elevated skeletal muscle mass which exert BP-increasing effects. This provides further support for the combined assessment of fat and lean mass in the risk evaluation of patients with ABCD.

2.5. Blood pressure and lung function

Although the underlying mechanisms are still incompletely understood, several studies have revealed significant interactions between systemic blood pressure and pulmonary function in across genders and ethnicities.

In a population-based prospective cohort study of Swedish men, hypertensive men with impaired lung function (height-adjusted FEV_1 below median) had significantly higher incidence of stroke, cardiac events and all-cause mortality than hypertensive group with high FEV_1, even after adjustment for smoking and other confounders (Engström *et al.*, 2001). Earlier, the Normative Age Study had demonstrated that residual FVC (adjusted for age and height) was inversely associated with 10-year incidence rate of hypertension in men (Sparrow *et al.*, 1988). Similarly, the multivariate adjusted 2-year risk of incident hypertension was significantly higher in initially normotensive Chinese women at the lowest quintiles of FEV_1 and FVC (Wu *et al.*, 1998). It has also been reported that older people with reduced FEV_1 display higher short-term beat-to-beat SBP variability (Engström *et al.*, 2009). Nevertheless, there is uncertainty over long-term association of impaired lung function and blood pressure variability. As indicated by the Jackson Heart Study, after multivariable adjustment, sex-specific quartiles of FVC and FEV_1 were not associated with day-night standard deviation and average real variability of SBP and DBP in African Americans (Booth III *et al.*, 2016).

Besides baseline records, the rate of FVC decline is a predictor of developing hypertension later in life. The prospective Coronary Artery Risk Development in Young Adults (CARDIA) Study showed that, controlling for sociodemographic,

SBP, and BMI data, young adults with greatest FVC decline from the peak recorded value were respectively 37% (HR:1.37 (1.05–1.80)) and 49% (HR:1.49 (1.07–2.07)) more likely to develop hypertension at year 10 and 20 follow-ups. Further, the risk of incident hypertension increased by 15% (HR:1.15 (1.06–1.26)) and 28% (HR: 1.28 (1.16–1.42)) per 1SD decrement of FVC from peak to years 10 and 20, respectively(Jacobs Jr *et al.*, 2012).

In this setting, one of the most plausible explanations would be the concomitant but not necessarily interconnected changes in the physiology of respiratory and vascular systems induced by or associated with adiposity and insulin resistance. Multidimensional influences of adiposity on respiratory function and systemic blood pressure were explored in previous sections.

With respect to insulin resistance, insulin can trigger polarisation of the effector T cells towards a Th2 phenotype, a key contributor to the pathogenesis of asthma. This hormone also induces mast cell-mediated bronchoconstriction by activating phosphoinositide 3-kinase (PI3K) pathway. As seen in patients with diabetes who had been administered inhaled insulin formulations, these substantial local effects may decrease FEV_1.

By synergistic interaction with insulin-like growth factor (IGF)-1 receptor, insulin may increase airway smooth muscle mass via mitogen-activated protein kinase (MAPK) - extracellular signal-regulated kinases (ERK) and PI3-K/Akt signalling pathways. Insulin also affects contractility of airway smooth muscles in a Rho kinase and PI3-kinase-dependent fashion. Rho-kinase pathway results in the production of contractile prostaglandins in airway smooth muscles. On this basis, insulin contributes to the formation of stiff and hypercontractile airways. Alternatively, insulin may modulate lung morphogenesis prenatally and airway remodelling postnatally via activation of Wnt / Beta-Catenin signalling (Singh *et al.*, 2013).Finally, it has been revealed that central hyperinsulinemia may increase hyperreactivity of both proximal and distal airways via activation of ERK but not PI3K/Akt pathway in parasympathetic pre-ganglionic nerves at the dorsal vagal complex (DVC) which convey outflow signals down to richly innervated small diameter airways where maximum contraction occurs (Leiria *et al.*, 2015).

Regarding the link between IR and systemic BP, there is compelling evidence that IR induces vascular dysfunction by impairing NO synthesis, activating MAPK-related vasoconstriction, inflammation, and sodium retention, and raising intracellular ICAM and VCAM levels following excessive release of prothrombotic and pro-inflammatory factors (Ormazabal *et al.*, 2018). In addition, IR is associated with the overactivity of SNS and RAAS, promoting myocellular hypertrophy and remodelling of the vessel wall (Landsberg, 1999).

Apart from the potential role of adiposity, systemic inflammation, and insulin resistance associated with abnormal changes in pulmonary function and systemic blood pressure, It could be postulated that diminished elastic recoil, airway remodelling and inflammatory reactions in lung parenchyma are directly associated with parallel nonatherosclerotic decline in elasticity and increased stiffness of the vessels together with endothelial dysfunction, and subsequently essential hypertension (McAllister *et al.*, 2007; Mills *et al.*, 2008).

Although the bulk of evidence points to the precedence of reduced lung function over hypertension, some studies have suggested a reverse relationship. In the ECRHS-I (European Community Respiratory Health Survey) Erfurt study, after adjustment for confounders, medically treated patients with uncontrolled hypertension had significantly lower FVC (-190ml) and FEV_1 (-150ml) compared to normotensive subjects or patients who did not receive antihypertensive medication (Schnabel, Nowak, *et al.*, 2011). Longstanding elevated BP causes LVH and raises the arterial and pulmonary venous pressure. This, in turn, leads to the interstitial fluid accumulation in lung parenchyma, reducing lung volume and compliance. Broncho-constrictive effects of β-blockers and angiotensin converting enzyme inhibitors (ACEI) may also aggravate the deterioration in lung function. This complies with the results of the Cardiovascular Health Study which showed that never-smoking elderly people free of pulmonary disease but with systolic hypertension had significant anthropometrically adjusted decrements in FEV_1 (-40 to -100-ml) and FVC (-50 to -150ml) as compared to their normotensive counterparts. Importantly, LVH is associated with significant declines in FVC and FEV_1 (Enright *et al.*, 1995). Arterial stiffness may also play a role in the association between elevated BP and reduced lung function. As revealed in the Multi-Ethnic Study of Atherosclerosis (MESA), multivariable adjusted FVC increased by 40±5

ml per 1SD increment in small arterial elasticity (SAE). Remarkably, endothelial (soluble intercellular adhesion molecule (sICAM-1), haemostatic (fibrinogen), and general inflammatory (hs-CRP and IL-6) biomarkers were all predictors of reduced SAE and FVC in men and women (Duprez *et al.*, 2013).

Altogether, it can be construed that there should be a common process linking impaired lung function, arterial stiffness, endothelial dysfunction, hypertension and cardiovascular events.

Chapter 3

Methodology

3.1. Study design and population

This research project was a cross-sectional study of community dwelling adults (19-65 years old) living in London. It was conducted in the Nutrition Physiology Laboratory at London Metropolitan University from November 2016 to October 2018. Ethical approval was taken from the School of Human Sciences ethics panel, London Metropolitan University (Appendix A). The study was not funded by any internal or external sources.

Recruitment process (Figure 3.1) involved advertisements on bulletin boards, the official website of the university, social networking sites. The project was also advertised in the student support services, the centre for education and learning, and the Science Centre. In addition, flyers (Appendix B) were distributed across the campuses (notice boards, cafeterias and outside lecture rooms, international student office, and the student hub). There were negotiations with the student union to notify student academic representatives, success coaches, society members, student council and related committees both internally and externally; communication with the schools and course leaders to inform their colleagues and students of this project. Promotion of the study was also undertaken across Barnet -Enfield-Haringey NHS services as well as minority ethnic communities. The recruitment process also included snowballing whereby the interested volunteers were asked to pass on details of the study to others via spoken word, email, or social networks. Induction sessions were held at the Tower Building, North Campus, London Metropolitan University where the potential participants were briefed about the project and the information sheets were distributed among them (Appendix C) to give the attendees a better understanding of the study. The interested volunteers (n=134) were given specific numbers. Then, 50% of the volunteers were selected randomly using random number generation. Selected individuals were contacted to arrange the measurements. Afterwards, supplementary information and preparatory instructions

about the tests were emailed to them three days before their appointments. A number of selected subjects (n=11) missed the appointment for different reasons (did not agree to perform the tests, did not show up, cancelled the appointment, developed one of the conditions precluding accurate measurements, could not access the site, rescheduled but failed to attend the session). In total, 56 adult men (n=25) and women (n=31) from students and staff of London Metropolitan University as well as the external volunteers took part in the study. The estimated sample size based on a priori calculation for hierarchical multiple linear regression was 83. Each participant was examined and tested during a pre-booked one-hour six-component session. The study consisted of sphygmomanometry, anthropometry, handgrip dynamometry, bioelectrical impedance analysis (BIA), air displacement plethysmography (ADP), and spirometry, carried out in a sequential order. At the beginning of the session, a brief description of the study and measurement techniques was given to the study participant (SP) and a written consent form was taken (Appendix D).

All procedures were done in accordance with national and/or international guidelines and the calibration, maintenance, quality control, cleaning, disinfection, and troubleshooting were undertaken based on the instructions provided by the manufacturers.

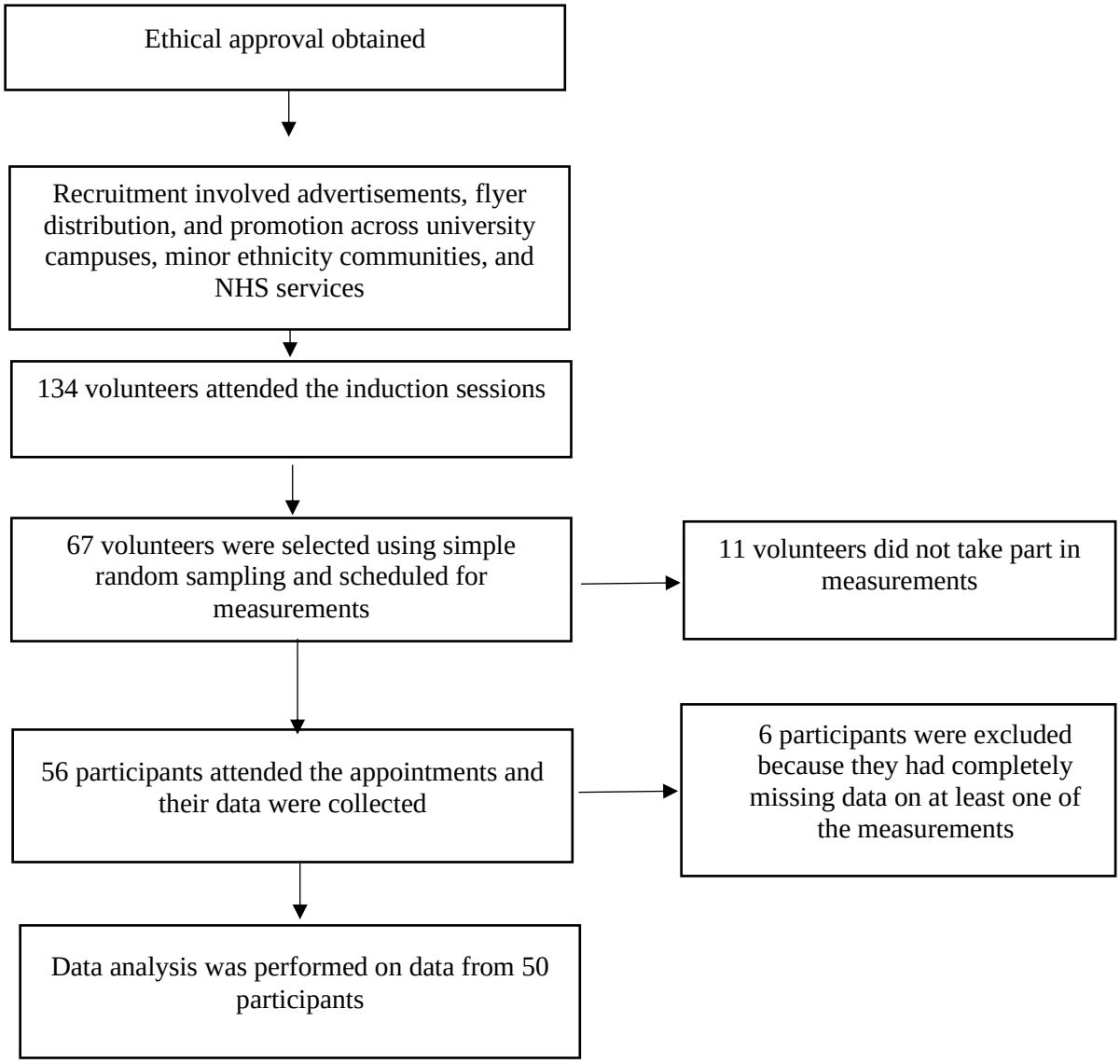


Figure 3.1. Flowchart of the study process

3.2 Study instruments and protocols

3.2.1 Anthropometry

General notes

The examiner explained the procedure to the SP before measuring any part. All circumference (except arm circumference) measurements were performed by SECA 201 ergonomic girth measuring tape (SECA GmbH & Co., KG, Hamburg, Germany), with eyes looking straight ahead. Measurements were taken with the examiner standing on the right side of the SP. At all times, the tape was kept parallel to the ground, perpendicular to the long axis of the SP's body part and pulled snugly without compressing the skin. The SP was instructed to turn in the direction needed for a given measure not the examiner. Before recording the value, it was ensured that the zero end of the tape was placed underneath the measured section. Parallax was avoided by reading the measurement in a line of sight directly in front of the value. All measurements were recorded to the nearest 1 centimetre. All circumference and height measurements were done two times and the average was used in the data analysis. A third measurement was undertaken if there was ≥ 1cm discrepancy between records.

Mid upper arm circumference and waist to hip ratio were determined by the BIA equipment.

Height

Height (Ht) was measured by Marsden HM-250P Portable Leicester Stadiometer (Marsden Weighing Machine Group Ltd., Rotherham, UK) in erect posture. At the beginning of each measurement, the stadiometer was calibrated by a 100cm rod. SP was asked to remove the shoes as well as any hair ornaments, braids, or buns from the top of the head. SP stood up straight against the vertical scale with the body weight evenly distributed, shoulders relaxed, arms hanging loosely by the side of body, legs straight, both feet flat on the floor plate, knees and heels together and toes apart, pointing 60 degrees outward. Care was taken to ensure the back of the head, shoulder blades, buttocks, and heels were in contact with the vertical scale. Then, the head was positioned in the Frankfort plane (a craniometric reference plane passing from the external auditory meatus to the inferior orbital margin), parallel to

the floor and perpendicular to the vertical backboard. During deep inspiration, the stadiometer headpiece was lowered to rest firmly on top of the participant's head whilst a gentle upward pressure was applied on the mastoid prominence. After recording the value, the subject released the breath. Measurement was considered non-straight (NS) if the SP had kyphoscoliosis, neck lesion, upper body weakness or any other problems that precluded an upright standing posture (Centre for Disease Control and Prevention, 2007).

Neck circumference

Neck circumference (NC) was measured in the midway of the neck between mid-cervical spine and mid-anterior neck (superior border of the tape just below the thyroid cartilage and perpendicular to the long axis of the neck) during inspiratory apnoea with the SP standing upright and the head positioned in the Frankfurt horizontal plane. The presence of any scars or swelling was noted and the history of neck surgery and thyroid disease was checked.

Waist circumference

Waist circumference (WC) was measured in the midabdominal location (midpoint between subcostal margin and superior border of iliac crest in midaxillary line) according to WHO protocol (World Health Organization, 2000). The examiner stood to the right side and behind the SP, with tape in his left hand. The examiner passed the tape around the SP's body with right hand, giving attention to the horizontal position of the tape. The SP was informed that the clothing could be lifted, and the trousers might be lowered to slightly below the waist. The measurement value was recorded at the end of the normal expiration. Ethnicity and sex specific thresholds for WC were defined (Table 3.1).

Table 3.1 Waist Circumference Thresholds for Abdominal Obesity as recommended by the international diabetes federation (IDF)(Alberti, Zimmet and Shaw, 2007)

Population	Men	Women
Europid	≥ 94 cm	≥ 80 cm
Middle East or East Mediterranean*	≥ 94 cm	≥ 80 cm
Black (African and African-Caribbean) *	≥ 94 cm	≥ 80 cm
Asian (including Chinese and South Asian)	≥ 90 cm	≥ 80 cm
Non-black Central and South American **	≥ 90 cm	≥ 80 cm

**European data until more specific data are available*

***South Asian recommendations until more specific data are available*

Thigh circumference

Thigh circumference (TC) was measured according to the National Institute for Health Research (NIHR) Southampton Biomedical Research Centre (BRC) Standard Operating Procedures. TC measurements were taken on the non-dominant side in mid-thigh area (at the mid-point between the anterior superior iliac spine and the lateral superior margin of the patella). The SP stood facing the examiner, with most of the weight on the dominant side. The SP held the non-dominant leg slightly flexed at knee joint and the soles of both feet flat on the floor. The tape was positioned perpendicular to the long axis of thigh, resting firmly on skin without indenting it (NIHR Southampton Biomedical Research Centre, 2015).

Calf circumference

Calf circumference (CC) was measured according to the NIHR Southampton BRC standard operating procedures on the non-dominant calf while the SP stood relaxed with the feet shoulder-width (about 25cm) apart and the body weight evenly distributed on both feet. The tape was extended horizontally around the calf at the widest part in a plane perpendicular to the long axis of the calf. As defined by WHO expert committee, a cut-point of 31cm was considered to be an indicator of low muscle mass (World Health Organization, 1995).

Computed parameters:

Body mass index (BMI) was calculated as Wt(kg)/ Ht $(m)^2$. Ethnicity-specific cut-off points were utilised for BMI classification (Table 3.2)

Table 3.2. WHO classification of body mass index (World Health Organization, 1995; 2004).

BMI classification	International	Asian
Underweight	<18.5	<18.5
Normal weight	18.5–24.9	18.5–22.9
Overweight	25-29.9	23-27.4
Obesity class I	30-34.9	27.5-32.4
Obesity class II	35-39.9	32.5-37.4
Obesity class III	>40	>37.5

Values are presented in kg/m^2

Waist to height ratio (WHtR) was calculated as WC/Ht to adjust for the variability in WC attributable to height. This measure has been shown to be a strong predictor of early health risks associated with excessive central adiposity (Ashwell and Gibson, 2016).

Neck to height ratio (NHtR) was calculated as NC/Ht. This ratio has been reported to be a predictor of sleep apnoea (Ho, Moul and Krishna, 2016) and metabolic syndrome (Selvan *et al.*, 2016).

Waist to calf ratio (WCR) was calculated as WC/CC. This ratio has been suggested to be a predictor of carotid atherosclerosis (Kim *et al.*, 2011).

Waist to thigh ratio (WTR) was calculated as WC/TC. This ratio has been suggested to be a predictor of hyperglycaemia and all-cause mortality (Mason, Craig and Katzmarzyk, 2008).

The new BMI (NBMI) was calculated as 1.3 × weight (kg)/height $(m)^{2.5}$ (van Vugt *et al.*, 2015), with 1.3 being the squared root of an assumed height (1.69 meter) for an average-sized adult. This formula can capture the gravity -related proportionality of transverse versus vertical growth more accurately because the body does not grow equally in all dimensions.

Overall, the squares of weight correspond to fifth powers of the height at different age. Switching to this new formula could be mathematically translated to 1unit BMI change per 30 cm of height if body weight remains unchanged (Trefethen, 2013). Thus, the revised equation may improve the discriminatory power of BMI equation (Amirabdollahian and Haghighatdoost, 2018).

Conicity index (CI) was calculated as WC(m)/0.109 * √(weight(kg)/ height (m)). This index adjusts WC by body size and has been proposed to be a predictor of long-term cardiovascular events (Valdez *et al.*, 1993).

A body shape index (ABSI) was calculated as WC/ (BMI $^{0.66}$× height (m)$^{0.5}$. This index accounts for the sublinear relationship between WC and BMI, along with its non-linear association with height, minimising the regression inflation caused by the multicollinearity of WC and BMI. ABSI has been shown to be associated with biochemical metabolic markers in young and healthy men with sedentary lifestyle (Malara, Anna and Tkaczyk, 2015) and a predictor of mortality risk in the general population (Krakauer and Krakauer, 2012).

3.2.2 Sphygmomanometry

Systolic and diastolic blood pressure were measured by OMRON M7 (HEM-780-E) automated oscillometric blood pressure monitoring device (OMRON Healthcare Co., Kyoto, Japan) in accordance with the American Heart Association (AHA) recommendations (Muntner *et al.*, 2019).

Exclusion criteria: both arms with skin lesions, dressings, plaster, major swelling or atrophy, open sores, or hematomas; the affected arm in SPs with a history of ipsilateral axillary nodal biopsy or resection.

Blood pressure (BP) was measured in the right arm. It was ascertained that SP had not taken caffeine or nicotine and had not exercised for at least 30 minutes before the measurement. SP rested quietly for 5 minutes prior to BP measurement; then BP was taken in a comfortable seated position, with legs uncrossed, back supported, arm bared (sleeve rolled up gently) and relaxed, the midpoint of the upper arm (halfway between the olecranon and acromion) kept at heart level (lower left sternal border in the fourth intercostal space), elbow slightly flexed, palm facing up, and

both feet flat on the floor. A properly sized cuff (cuff bladder encircling ≥80 and 40% of arm length and width, respectively) was wrapped snuggly around the arm (2cm above the antecubital fossa), with marked edging turned medially, and the air tube running parallel to the medial side of the forearm. Two successive measurements were done 3 minutes apart. SP sat still whilst SBP and DBP were being recorded automatically by the unit attached to the cuff). If two recordings differed by more than 20mmHg, an additional BP measurement was done.

Computed parameters

The mean arterial pressure (MAP) was calculated as (SBP+2DBP)/3 as a predictor of cardiovascular health (Sesso *et al.*, 2000).

Pulse pressure (PP) was calculated as (SBP -DBP) as an indicator of arterial stiffness (Jankowich, Taveira and Wu, 2009).

3.2.3 Dynamometry

The isometric grip strength was measured in both hands by Takei 5001 Analogue Grip Dynamometer (Takei Scientific Instruments Co., Niigata, Japan).

SPs with visible limitations or lesions on the hands (missing finger or phalange, congenital anomalies, broken or casted finger, wrist or hand, hand lesion, open sore, distal motor neuropathy or myopathy) or those with a history of hand or wrist surgery during a three-month period prior to test were excluded from the measurement. The history of wrist or hand arthritis, tendinopathy or tenosynovitis, or pain, aching or stiffness in hands in past 7 days was recorded.

The dynamometer was adjusted for grip size until the proximal interphalangeal (PIP) joint of the fingers were at 90˚ flexion, with the hand being in line with the wrist and forearm. If the second joint of the index finger was flexed less than 90 degrees, the adjustment knob was turned clockwise to increase the grip size. If the joint flexion was greater than 90 degrees, the grip size was decreased by turning the knob anticlockwise.

In compliance with the National Centre for Health Statistics (NCHS) protocol (National Center for Health Statistics, 2011), the test was performed in the upright

standing position. Having been explained the proper technique for the test, the SP grasped the dynamometer between the fingers and the palm at the base of the thumb. Holding the dynamometer in line with the forearm at the thigh level, the SP was asked to squeeze the dynamometer tightly and forcefully while breathing out, with shoulders, back and chest straightened, eyes straight ahead, shoulder abducted about 10 degrees, elbow fully extended, and wrist in neutral position. When the peak hold needle stopped rising, the reading was recorded in kilogram force units rounded to the nearest 1kg. The SP rested for 5 minutes between successive measurements.

Grip strength was defined as normal, intermediate and weak according to cut-points (Alley *et al.*, 2014) recommended by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project for the identification of clinically relevant weakness (Table 3.3).

Table 3.3. Grip strength thresholds for clinical weakness adopted from (Alley *et al.*, 2014)

Cut-off point	**Men**	**Women**
Normal	≥32 kg	≥20 kg
Intermediate	≥26 but <32kg	≥16 but <20kg
Weak	<26kg	<16kg

3.2.4 Body composition assessment

Body composition was assessed by air displacement plethysmography and bioelectrical impedance direct segmental multifrequency body composition analysis (DSM-BIA) methods.

3.2.4.1 Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) was conducted by Tanita MC 980 MA (Tanita Co., Inc, Tokyo, Japan) and InBody 720 (InBody Co., Ltd., Seoul, Korea), each operating on a tetrapolar 8-point tactile electrode system that measured the impedance (resistance and reactance) in the limbs and trunk and, as explained earlier in the literature review, determined total body water (TBW), fat-free mass (FFM), and fat mass (FM) as well as segmental lean and fat mass from impedance, height, and weight included in patented prediction equations.

Exclusion criteria: Any metallic part (e.g., pacemaker, defibrillator, nerve stimulator), prosthetic joints or pins, catheters, renal failure, serious life-limiting comorbid situations (such as malignancy, uncontrollable infection, and end-stage heart, lung, or liver disease), pregnancy or lactation, taking diuretics or lipid-lowering agents, active oozing hand and foot skin lesions, hyperhidrosis, generalised oedema.

Cautions before measurements:

A few days prior to the appointment, the SP was advised not to have a meal less than 2 hours before the test, to avoid the test during menses, not to exercise or bath before the test. The SP was also instructed to use the bathroom, wear light clothes, remove jewellery or other ornamental objects, and not sit down or stand up before starting the measurement.

Protocol

The SP stepped on the foot electrode barefooted and stood still comfortably with hands hanging down and heel and the ball of the feet touching the foot electrodes. After the record of body weight and personal information was completed, the SP held the hand electrodes gently. Attention was given to make sure palms, fingers and soles correctly touched the electrodes and heels landed on the circular-shaped foot electrode before the forefoot hit the front electrode without any piece of clothing getting in between the heels and electrodes. The shoulders were relaxed, arms abducted about 15 degrees, elbows and fully extended, and knees not flexed. If the SP's feet or hands were too dry, or had crusts, the palms and soles would wet with electrolyte tissue.

Computed parameters:

To examine relative contribution of fatness and leanness to the outcomes, fat mass to fat-free mass ratio was calculated as FM/FFM for both analysers.

To understand the comparative influence of limb fat and lean tissues on the outcomes, fat and muscle(lean) contents of 4 extremities were integrated to the composite appendicular fat mass (AFM) and appendicular muscle mass (ASM) or lean mass (ALM) as the sum of the corresponding values for each limb (right arm, left arm, right leg, and left leg).

To compare the associations of upper versus lower extremity fat, lean and skeletal muscle mass with the outcomes, corresponding terms were created as follows:

Upper limb fat mass (UFM) was calculated as the sum of right arm and left arm FM (RAFM+LAFM)

Upper limb lean mass (ULM) was calculated as the sum of right arm and left arm LM(RALM+LALM)

Upper limb skeletal muscle mass (USM) was calculated as the sum of right arm and left arm SMM (RAMM+LAMM)

Lower limb fat mass (LFM) was calculated as the sum of right leg and left leg FM (RLFM+LLFM)

Lower limb lean mass (LLM) was calculated as the sum of right leg and left leg LM (RLLM+LLLM)

Lower limb skeletal muscle mass (LSM) was calculated as the sum of right leg and left leg SMM (RLMM+LLMM)

To investigate the combined contributions of truncal versus appendicular fat and skeletal muscle masses to the outcomes, relative ratios were calculated as AFM/ASM, and truncal FM(TFM)/ truncal SMM(TSM),

To adjust for the variations in height the following indices were constructed:

Fat mass index (FMI) was calculated as FM/Ht^2 (kg/m^2) for both analysers.

Skeletal muscle mass index (SMI) was calculated SMM/ Ht^2 (kg/m^2) for Tanita MC 980 MA.

Corresponding indices were also computed for appendicular and truncal parameters as follows:

AFM index (AFMI)= AFM/ Ht^2 (kg/m^2)

ASM index (ASMI)= ASM/ Ht^2 (kg/m^2)

TFM index (TFMI)= TFM/ Ht^2 (kg/m^2)

TSM index (TSMI)= TSM/ Ht^2 (kg/m^2).

3.2.4.2 Air displacement plethysmography

Whole body densitometry was performed by the air displacement plethysmography (BODPOD) system (Life Measurement, Inc, Concord, CA, USA).

A few days prior to testing, the SP was advised to be dry and to refrain from shower for at least 1 hour before testing and not to grow facial hair or beard, not to wear "Boxer" or running shorts, and not to eat or exercise for 3-4 hours before testing (Fields, Higgins and Radley, 2005).

The BODPOD was warmed up for 30 minutes and the environment stability was verified, especially with respect to room temperature. Then the integrated digital weighing scale was calibrated by using two gold calibration weights (19.99 to 20.01 kg) to keep the reading precision at 0.01 kg of the weights. Then, the BODPOD was calibrated using a 50L cylinder. It was ascertained that the SP wore no jewellery or eyeglasses and was minimally clothed (tight-fitting or Spandex swimsuit or single-layer compression shorts and sport bras (without padding or wires)) and put on tight-fitting acrylic swim cap, ensuring that all hair was hidden under the cap. Any air pockets were released from under the cap. Having weighed the SP, the procedure was fully described. In addition to the exclusion criteria described for the BIA, the possibility of claustrophobia was ruled out before the test. The SP was assured that the test could be cancelled anytime by pressing the magnet release button. The SP sat comfortably in the BODPOD, hands in lap, breathing normally without talking or laughing. The test lasted approximately 40 seconds and was repeated one more time with 30-second intervals between tests. The system measured the uncorrected body volume based on volume changes inside the chambers (explained earlier in the literature review). In the event of disagreement between measurements (>150mls as set by the manufacturer), another measurement was carried out. After the completion of the test, the mean of the two closest measurements was used to determine the corrected body volume, body density (Db), %BF, FM, and FFM. The actual body volume was calculated by the system software after adjustment for the predicted lung volume (Collins and McCarthy, 2003) and body surface area artefact. The calculated Db (actual volume/body weight) was used to determine %BF according to Siri equation (Siri, 1961).

3.3 Spirometry

Lung function was evaluated by the COSMED Quark PFT modular system (COSMED s.r.l, Rome, Italy). This system consists of a Quark unit, a turbine flowmeter, breathing valve, and additional external sensors and devices. The expired gas is analysed by using an infrared optoelectronic reader counting the light interruptions caused by the spinning vanes of the bidirectional turbine. Technical features and accuracy specifications of the equipment comply with the ERS/ATS standards (Table 2.1).

Exclusion criteria (Miller, Crapo, *et al.*, 2005)

- Current painful ear infection
- Thoracic or abdominal surgery in the last 3 months
- Brain, eye, or ENT surgery in the last 3 months
- Pneumothorax
- Bronchial marked hypersensitivity
- Severe gas exchange impairment
- Myocardial infarction
- Aortic aneurysm
- Haemoptysis
- Pulmonary embolism
- Retinal detachment
- Acute diarrhoea
- Stroke or angina in the last 3 months
- Severe hypertension (systolic >200 mm Hg, diastolic >120 mm Hg)
- Confused patients

Protocol

Lung function testing was conducted according to the ATS/ERS task force recommendations (Miller, *et al.*, 2005). Prior to spirometry, the SP was asked to loosen any tight clothing and to remove dentures if they were not secure.

Spirometric testing was performed in the standing position but a stool was positioned behind the SP. Having been demonstrated the proper technique, the SP was instructed to lift the chin and extend the neck slightly. The flowmeter was attached to the handle to connect the turbine to Quark unit. Then the antibacterial filter was mounted onto the turbine. First, a trial test was practiced in the following manner: after deep inspiration, the SP put the disposable filter into the mouth, between teeth, and on top of tongue, bit on the filter lightly and sealed the lips tightly around it, applied nose clip, blasted out the air as hard and fast as possible, and continued forced expiratory manoeuvre for at least 6 seconds or until the SP could not carry on. The adequacy of the attempt was decided by the pattern of volume-time and flow-volume curves to detect submaximal inhalation, excessive extrapolated volume due to hesitated initiation, submaximal blast due to insufficient expiratory effort, jagged interruption due to coughing, early termination, dipped flow-volume curved due to variable exhalatory effort, abrupt cessation due to glottis closure or breath holding, curve descent after plateau or back-tracking toward zero due to air leak, stepped curve due to extra breath(s), or zero-flow errors due to incorrectly set flow references (for details see Chapter 2) (Beeckman-Wagner and Freeland, 2012). Three best attempts were considered for the analysis. The spirometric indices (FVC, FEV_1, FEV_1/FVC, $FEF_{25-75\%}$) were expressed in absolute values to avoid the inaccuracies of using percentage of the predicted values.

3.3 Statistical analysis

The sample size (n=83) was calculated using a priori power analysis by the statistical software package G*Power 3.1 (Faul *et al.*, 2009). The F test procedure was chosen to determine sample size based on the r^2increases in a multiple linear regression model given the alpha level of 0.05 and power of 80%, with 7 predictors and an estimated effect size (partial r^2) of 0.16.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS Inc., Chicago, IL, USA). Because of 14% (>10%) missingness and the small sample size, even though the data were missing completely at random, multiple imputation was carried out to replace the missing values by the simulated values (predicted from the observed cases) with the highest

possible similarity to the available data to reduce bias in parameter estimations (Sterne *et al.*, 2009). First, monotonicity of the missing values was ruled out in the pattern analysis chart where concentrations of missing datapoints touching to the upper left and lower right were interspersed by patches of non-missing datapoints, indicating a random pattern of missingness and low chance of bias. Then the random seed settings were determined by Mersenne Twister method to initialise random number generator. Subsequently, all variables with missing values were entered in the imputation model (5 simulations per sequence of missing data) to create a new complete data set with the average of newly imputed values replacing corresponding missing values by the fully conditional specification (Markov Chain Monte Carlo (MCMC)) imputation method(Rubin and Schenker, 1991). Due to the small size of the study sample ($n \leq 50$) and mild missingness ($\leq 20\%$), predictive mean matching (PMM) method was chosen as the preferred type of the regression model (Barnes, Lindborg and Seaman Jr, 2006) as it could provide imputed values consistent with observed values

The imputed data were almost normally distributed (as checked by Shapiro-Wilk test of normality, skewness statistics and visual inspection of histograms). Body composition phenotypes were created by transforming raw values into tertiles and by constructing composite variables that integrated corresponding total and segmental fat and lean mass. The presence of outliers was inspected graphically (Box plots) as well as statistically (using the interquartile range formula). The significance value was set at $p<0.05$. To create composite variables, syntax codes were utilised. Bivariate relationships among anthropometric, body composition and spirometric measures were examined by Pearson's correlation test. The association between body composition and lung function across levels of systemic blood pressure was explored using general linear models meeting the assumptions of linearity and normality of residuals. The assumption of homoscedasticity (equality of residual variances) was examined by the modified Breusch -Pagan test (Breusch and Pagan, 1979) and heteroscedasticity consistent standard errors were estimated using SPSS macros (Hayes and Cai, 2007) when required. Statistical significance was set at a p-value<0.05. Post-hoc analyses were done by Tukey's honest significant difference (HSD) test (Tukey and Cleveland, 1984). The effects of the moderators on the association between the predictors and outcomes were

investigated in the PROCESS macro version 3.2 (Hayes, 2012) using simple moderation analysis (in the form of an ordinary least squares (OLS) regression) whereby the outcome would be estimated as a weighted function of the predictors and their interaction. Bias-corrected 95% confidence intervals were also generated by bootstrapping. The heteroscedasticity consistent standard error estimator developed by MacKinnon & White was chosen to yield robust inferences on the OLS parameter estimates (Hayes and Cai, 2007). To probe the significant interactions, the conditional effect of the independent variable on the outcome variable was estimated at various (low, medium, and high) levels of the moderating predictor operationalised respectively as 16th, 50th and 84th percentiles. To demarcate regions of significance of the effect of predictors on the outcomes along the continuum of the moderators, the Johnson-Neyman technique (Hayes and Matthews, 2009) was utilised. This technique delineates the values of moderator where the conditional effect transitioned from significance to non-significance as well as the confidence interval bands for the regression slopes. The conditional effects of the predictors on the outcomes at three discrete percentiles of the moderator were visually depicted as the interaction plots using the output table for data visualisation generated by the PROCESS.

3.4 Descriptive Characteristics

The main characteristics of the study population are presented in Tables 3.3 to 3.6. In total, 22 men and 28 women aged 22 to 61 years took part in the study. Participants were ethnically diverse (10 British white, 27 non-British white, 3 black, 6 South Asian, 2 Asian, 1 Hispanic, and 1 white-Asian), predominantly non-smoker (32 never-smokers, 13 ex-smokers, and 2 current-smokers), physically active (37 moderately active, 7 vigorously active, 5 lightly active, and 1 sedentary lifestyle), and healthy/overfat (20% under-fat, 40% healthy, 40% overfat) with normal grip strength (100%) and no history of pulmonary, cardiovascular or neuromuscular diseases . In general, female SPs had lower BMI, NC, AC, WC, TC, CC, WHR, and WHtR as well as total (FFM, LBM, SMM) and segmental (ALM, ASM, ULM, USM, LLM, LSM) lean mass. In comparison, total fat (%BF and FM) and appendicular fat (AFM and LFM) were proportionally higher in females while their

centrally distributed fat was significantly lower than males. However, UFM was not significantly different between sexes. Male SPs had stronger grips, higher SBP, wider pulse pressure, larger LV and higher FVC, FEV_1, and $FEF_{25-75\%}$. FEV_1/FVC ratio was lower in males; there was no significant difference in DBP between male and female SPs.

Table 3.4. Age and anthropometric measures

	Male	**Female**	**Total**
Age	38.00±13.13	35.21±8.90	36.44±10.93
Ht (cm	177.42±7.57	165.67±6.24	170.84±8.99
Wt (kg)	79.14±10.21	59.30±7.13	68.03±13.10
BMI (kg/m^2)	25.24±2.89	21.62±2.46	23.21±3.19
NC (cm)	38.69±2.99	32.93±2.70	35.47±4.02
AC (cm)	32.86±2.71	28.87±2.68	30.63±3.33
WC (cm)	87.73±9.81	73.60±7.27	79.82±10.98
TC (cm)	48.19±2.90	46.24±3.19	47.10±3.19
CC (cm)	37.50±2.31	34.93±2.10	36.06±2.53
WHR	0.90±0.06	0.83±0.07	0.86±0.07
WHtR	0.49±0.07	0.44±0.05	0.47±0.06
NBMI	24.60±3.00	21.86±2.61	23.06±3.08
WTR	1.85±0.22	1.60±0.15	1.71±0.23
WCR	2.33±0.21	2.10±0.18	2.20±0.22
NHtR	0.22±0.02	0.20±0.02	0.21±0.02
CI	0.017±0.001	0.016±0.001	0.017±0.001
ABSI*	335.31±33.00	354.54±26.66	346.08±30.84

Values are presented as mean ± SD

For all variables in male, female, and total participants, n=22, 28, and 50, respectively.

Wt: body weight(kg); BMI: body mass index; NC: neck circumference; AC: arm circumference; WC: waist circumference; TC: thigh circumference; CC: calf circumference; WHR: waist to hip ratio; WHtR: waist to height ratio. NBMI: new BMI; WTR: waist to thigh ratio; WCR: waist to calf ratio; NHtR: neck to height ratio; CI: conicity index; ABSI: a body shape index.

Table 3.5. Sex and ethnicity-specific adiposity status

	Male	**Female**	**Total**
BMI-defined			
Underweight	0	2 (7%)	2 (6%)
Normal weight	11 (50%)	20 (71%)	31 (62%)
Overweight	8 (36%)	6 (21%)	14 (38%)
Obesity	3 (14%)	0	3 (4%)
WC-defined			
No abdominal obesity	16 (73%)	25 (89%)	41 (82%)
Abdominal obesity	6 (27%)	3 (11%)	9 (8%)
BODPOD-defined			
Underfat	1 (4%)	9 (32%)	10 (20%)
Healthy	9 (41%)	11(39%)	20 (40%)
Overfat/obesity	12 (55%)	8 (29%)	20 (40%)

Values are presented as frequency (%)

BMI definition follows WHO criteria for general and Asian population (World Health Organization, 1995; 2004)

WC definition follows IDF ethnicity-specific thresholds for abdominal obesity (Alberti, Zimmet and Shaw, 2007)

Fatness status is defined according to BMI, age, sex, and ethnicity-specific body fat ranges recommended by Gallagher et al. (Gallagher et al., 2000)

Table 3.5. Body composition measurements

	Body composition	Male	Female	Total
Lean segment	FFM Tanita (kg)	62.56±8.94	45.86±5.05	53.21±10.88
	FFM InBody (kg)	63.58±7.36	45.93±5.15	53.70±10.78
	FFM BODPOD (kg)	61.50±7.56	45.27±5.82	52.41±10.46
	SMM InBody (kg)	35.43±5.39	26.00±3.67	30.15±6.49
	TSM (kg) ***	32.72±3.78	25.76±2.36	28.82±4.63
	ASM (kg) ***	27.19±1.45	19.10±.2.52	22.66±5.28
	USM (kg) ***	7.03±1.29	4.28±0.73	5.49±1.71
	LSM (kg) ***	20.60±2.28	14.71±1.60	17.30±3.52
Fat segment	%BF InBody	20.44±8.48	24.39±6.66	22.65±7.69
	%BF Tanita	19.58±6.76	24.33±5.19	22.24±6.33
	%BF BODPOD	22.29±8.43	25.36±6.45	24.01±7.47
	FM InBody (kg)	16.76±8.02	14.78±5.15	15.65±6.57
	FM Tanita (kg)	15.63±6.42	15.19±4.55	15.38±5.40
	FM BODPOD (kg)	18.01±7.89	15.26±4.76	16.47±6.41
	VFA (cm^2) *	86.63±56.67	61.16±30.59	72.37±45.33
	VFR*	6.64±4.75	3.12±2.17	4.67±3.92
	TFM (kg)	9.49±4.50	6.94±2.80	8.06±3.83
	AFM (kg)	5.96±2.27	8.36±2.13	7.31±2.48
	LFM (kg)	4.42±1.75	6.76±1.78	5.73±2.11
	UFM (kg)	1.57±0.59	1.52±0.51	1.55±0.54

Values are presented as mean ± SD

For all variables in male, female, and total participants, n=22, 28, and 50, respectively.

FFM: fat free mass; SLM: soft lean mass; LBM: lean body mass; SMM: skeletal muscle mass; TSM: trunk muscle mass; ASM: appendicular skeletal muscle mass; USM: upper limb skeletal muscle mass; LSM: lower limb skeletal muscle mass; BF: body fat; FM: fat mass; VFA: visceral fat area; VFR: visceral fat rating; TFM: trunk fat mass; AFM: appendicular fat mass; UFM: upper limb fat mass; LFM: lower limb fat mass.

Table 3.6. Grip strength, measures of blood pressure, and spirometric indices

	Male	**Female**	**Total**
Grip R (kg)	44.00±12.00	30.50±3.75	33.19±12.63
Grip L (kg)	41.50±7.00	30.00±6.00	33.00±10.25
Grip M (kg)	42.25±8.63	30.00±4.38	33.25±11.28
SBP (mmHg)	118.07±10.38	108.25±12.67	112.62±12.59
DBP (mmHg)	74.98±11.14	75.50±11.50	74.84±11.22
PP (mmHg)	43.09±9.33	35.50±8.51	37.83±9.97
MAP (mmHg)	89.34±9.96	86.08±11.26	87.51±10.73
LV (L)	4.06±0.36	3.36±0.35	3.67±0.50
FVC (L)	4.81±1.21	3.31±0.63	3.97±1.19
FEV_1 (L)	4.35±0.85	3.14±0.51	3.67±0.91
FEV_1/FVC	88.59±5.46	94.17±4.58	91.72±5.67
$FEF_{25-75\%}$ (L/s)	5.08±1.24	4.31±0.90	4.65±1.12

Values are presented as mean ± SD

For all variables in male, female, and total participants, n=22, 28, and 50, respectively.

Grip strength records are presented as median ± IQR; measures of blood pressure are presented as mean ± SD. Grip M: average grip strength of both hands; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure. LV: lung volume; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25-75\%}$*: forced expiratory flow at 25–75% of FVC.*

Chapter 4

Anthropometric Measures and Body Composition

To understand which anthropometric measures are better indicators of fat-free mass and/or fat mass at total and segmental level, the anthropometric measurements were divided into conventional and non-conventional categories. Conventional anthropometric measures included BMI, NC, AC, WC, TC, CC, WHR, and WHtR. Non-conventional anthropometric measures included NBMI, WTR, WCR, NHtR, CI, and ABSI. The relationships between these measures and body composition data derived from segmental BIA and the BODPOD system were examined using Pearson's correlation test. BIA-derived parameters included FFM, SMM, TSM, ASM, USM, LSM as well as %BF, FM, VFA, TFM, AFM, UFM, LFM. Body composition parameters determined by the BODPOD system included FFM_{ADP}, $\%BF_{ADP}$, and FM_{ADP}. These parameters (except %BF) were also divided by the square of height to create stature-adjusted indices of total and segmental body composition to account for the contribution of height to the variability in FM and FFM. The expression of fatness and leanness as the indices normalised for body size has been shown to provide more accurate information about the nutritional and health status of the individuals of different age, sex and body size as compared to the expression of FM and FFM as absolute or relative (percentages of weight) values (Schutz, Kyle and Pichard, 2002).

Results

4.1 Total Lean mass and anthropometric measurements

As shown in Table 4.1, NC and AC were the strongest conventional anthropometric correlates of FFM, FFM_{ADP}, and SMM followed by WC, CC and BMI in the entire study population. In male SPs, AC was significantly correlated with FFM and SMM but not FFM_{ADP}. NC showed significant correlations with SMM. No significant correlation was found between other indices and total lean mass.

Table 4.1. Conventional anthropometric measures and leanness

	Total and Segmental lean mass (kg)	Conventional anthropometric measures							
		BMI	NC	AC	WC	TC	CC	WHR	WHtR
Male	FFM	0.37	0.48*	0.68***	0.26	0.31	0.45	0.17	0.04
	FFM_{ADP}	0.13	0.36	0.42	0.03	0.08	0.32	-0.05	-0.19
	SMM	0.13	0.43	0.58**	0.01	0.27	0.42*	-0.11	-0.27
	TSM	0.42	0.57**	0.73***	0.34	0.32	0.47*	0.26	0.10
	ASM	0.27	0.35	0.57**	0.17	0.21	0.39	0.05	-0.04
	USM	0.28	0.38	0.61**	0.12	0.36	0.29	0.06	-0.07
	LSM	0.27	0.31	0.57**	0.16	0.25	0.49*	0.02	-0.08
Female	FFM	0.02	-0.08	0.11	-0.14	-0.06	-0.17	-0.01	-0.11
	FFM_{ADP}	0.16	0.33	0.26	0.36	0.35	0.40*	0.15	0.16
	SMM	-0.05	0.42*	0.19	0.03	-0.23	-0.07	0.14	-0.07
	TSM	0.11	-0.02	-0.05	-0.02	.01	-0.08	0.02	-0.05
	ASM	-0.08	-0.17	-0.19	-0.23	-0.15	-0.27	-0.08	-0.21
	USM	0.02	-0.09	-0.12	-0.05	-0.04	-0.06	0.01	-0.07
	LSM	-0.18	-0.24	-0.26	-0.32	-0.18	-0.27	-0.15	-0.31
Total	FFM	0.57***	0.68***	0.64***	0.58***	0.32*	0.51***	0.37*	0.35*
	FFM_{ADP}	0.52***	0.72***	0.64***	0.59***	0.36*	0.59***	0.36*	0.32*
	SMM	0.45**	0.73***	0.66***	0.49***	0.25	0.50***	0.32*	0.22
	TSM	0.59***	0.69***	0.66***	0.59***	0.34*	0.52***	0.39*	0.36*
	ASM	0.53***	0.64***	0.60***	0.54***	0.28	0.49**	0.33	0.31*
	USM	0.54***	0.66***	0.62***	0.55***	0.34*	0.49**	0.35*	0.32*
	LSM	0.50***	0.62***	0.57***	0.52***	0.27	0.49**	0.31	0.28

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

BMI: body mass index; NC: neck circumference; AC: arm circumference; WC: waist circumference; TC: thigh circumference; CC: calf circumference; WHR: waist to hip ratio; WHtR: waist to height ratio; FFM: fat free mass; SMM: skeletal muscle mass; TSM: trunk muscle mass; ASM: appendicular skeletal muscle mass; USM: upper limb skeletal muscle mass; LSM: lower limb skeletal muscle mass;

The only significant findings in female SPs were the correlations of CC with FFM_{ADP} and AC with FFM (Table 4.2), ABSI and CI were stronger correlates of

FFM, FFM_{ADP}, and SMM in the total population. Of note, the ABSI was the only significant non-conventional correlate of FFM, FFM_{ADP}, and SMM in male SPs. It showed a consistently negative relationship with all measures of total lean mass in men and women.

Table 4.2. Non-conventional anthropometric measures and leanness

	Total and Segmental lean mass (kg)	**Non-conventional anthropometric measures**					
		NBMI	WTR	WCR	NHtR	CI	ABSI
Male	FFM	0.25	-0.10	-0.25	-0.09	-0.11	-0.79***
	FFM_{ADP}	0.02	-0.12	-0.17	-0.13	-0.13	-0.78***
	SMM	-0.01	-0.10	-0.24	0.01	-0.10	-0.80***
	TSM	0.29	0.17	0.10	0.25	0.17	-0.46*
	ASM	0.16	0.08	-0.05	0.03	0.05	-0.52*
	USM	0.17	-0.03	-0.04	0.08	-0.03	-0.54*
	LSM	0.15	0.06	-0.13	-0.05	0.04	-0.59*
Female	FFM	0.02	0.24	0.11	0.11	0.20	-0.42*
	FFM_{ADP}	0.07	0.24	0.13	0.12	0.20	-0.37
	SMM	-0.09	0.19	0.07	0.31	0.07	-0.19
	TSM	0.09	-0.05	0.01	-0.06	-0.14	-0.23
	ASM	-0.06	-0.15	-0.08	-0.14	-0.28	-0.17
	USM	0.08	-0.05	-0.04	-0.12	-0.11	-0.16
	LSM	-0.16	-0.22	-0.19	-0.23	-0.34	-0.25
Total	FFM	0.44**	0.41**	0.31*	0.38**	0.55**	-0.63***
	FFM_{ADP}	0.38**	0.40**	0.37*	0.37*	0.53**	-0.62***
	SMM	0.31*	0.40**	0.30*	0.45**	0.46**	-0.58***
	TSM	0.46**	0.46**	0.41**	0.45**	0.55**	-0.47**
	ASM	0.40**	0.44**	0.37*	0.39**	0.53**	-0.46**
	USM	0.41**	0.41**	0.38*	0.41**	0.52**	-0.47**
	LSM	0.37*	0.42**	0.33	0.35*	0.53**	-0.49***

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

NBMI: new BMI; WTR: waist to thigh ratio; WCR: waist to calf ratio; NHtR: neck to height ratio; CI: conicity index; ABSI: a body shape index. FFM: fat free mas; SMM: skeletal muscle mass; TSM: trunk muscle mass; ASM: appendicular skeletal muscle mass; USM: upper limb skeletal muscle mass; LSM: lower limb skeletal muscle mass.

4.2 Segmental lean mass and anthropometric measurements

AC and NC were the strongest conventional anthropometric correlates of truncal, appendicular, lower limb, and upper limb lean/skeletal muscle mass in total population whereas TC, WHtR and WHR demonstrated weakest correlations. AC and NC were most strongly correlated with TSM, respectively. Stratified by sex, AC was the only conventional measure that showed significant correlations with the abovementioned indicators of segmental lean mass in male SPs. AC was most strongly correlated with TSM (Table 4.1). WHtR and WHR displayed negative (but weak) correlations in both sexes. Among the non-conventional anthropometric indices (Table 4.2), NBMI and ABSI showed the strongest correlations with all segmental measures of lean mass in total population, albeit in opposite directions. WTR and CI where equally correlated with segmental lean mass. Split by sex, the ABSI was the only significant non-conventional anthropometric correlate of segmental lean mass in men. It exhibited inverse relationships with measures of segmental lean mass. Compared with commonly used anthropometric indices, the ABSI was a stronger correlate of lower body lean mass in men. In women, non-conventional anthropometric indices were weakly correlated with segmental lean mass. The ABSI exhibited the most consistent negative relationship with segmental lean mass in both sexes.

Collectively, AC and NC were the strongest anthropometric correlates of total leanness together with total, truncal and appendicular muscularity whilst ABSI was the only anthropometric index which was inversely and significantly related to total and segmental leanness/muscularity in the entire study population. Thus, large arm and neck circumferences may indicate expanded lean or muscular tissues better than other anthropometric measures in free-living healthy adults. It is worth mentioning that the anthropometric measures commonly used as the indicators of fatness had directly significant relationships with BIA-derived fat-free mass and skeletal muscle mass, underscoring the contribution of lean compartments to the associations observed between these measures (BMI, WC, WHR, WHtR) and metabolic risk factors. In this regard, increased ABSI (as an index of body-size adjusted WC) could be an indicator of depleted lean mass.

As the study was underpowered for subgroup analysis, it is difficult to make inferences about the sex-specific relationships between anthropometric indices and measures of leanness.

4.3 Total body fat and anthropometric indices

In total, WHtR, BMI, and WC were the strongest conventional anthropometric correlates of total fat mass whereas WHtR and BMI were stronger correlates of %BF. After sex stratification, WHR, WHtR, WC and BMI were strongly correlated with FM and %BF in male SPs. No significant relationship was found between either %BF or FM with TC, AC, and NC in total and male SPs. NC showed the weakest correlation with %BF while TC was the weakest correlate of FM. In female SPs, however, BMI, AC, WC, and WHtR were strong correlates of FM and %BF. Although, %BF by the BODPOD was significantly correlated with BMI and WHtR. TC was the weakest correlate of total body fat in this group (Table 4.3).

Among the non-conventional measures, NBMI was the only significant anthropometric correlate of total body fat in total SPs. This index was the strongest correlate of FM and BF% in men and women too. WTR and CI also demonstrated moderate to strong relationships with total body fat in men. The strength of correlation was lower in women. The ABSI did not show any significant correlation with FM or %BF in female SPs (Table 4.4). Taken together, NBMI and BMI were comparably correlated with FM and BF% in both sexes.

4.4 Segmental body fat and anthropometric indices

In the entire study population, visceral fat was most strongly related to WHtR, WC, WHR, and BMI. WC, BMI, WHtR and WHR were respectively the strongest correlates of truncal fat. Upper limb fat mass was most strongly correlated with BMI and WHtR followed equally by WC and WHR. All these measures showed comparably strong relationships with VFA. None of the conventional anthropometric measurements had significant correlation with the fat content of the lower limb. In men, the strongest correlates of VFA were WHR, WHtR, and WC, while in women BMI, AC, and WHtR exhibited the strongest correlations. WHR and WC were equally correlated with VFA in females. For TFM, WC and WHR

were the strongest correlates in male SPs. In female SPs, BMI, WC and WHR were the only significant correlates of TFM. While AFM was most strongly correlated with BMI, WHR and WC and in men, it showed the strongest correlations with BMI and WC in women. Relatively similar sex-specific patterns were detected for the correlations of UFM and LFM with the conventional anthropometric measures, with BMI, WC and WHR being the strongest correlates in male SPs and BMI, WC and WHtR being the strongest correlates in female SPs (Table 4.3).

As shown in Table 4.4, NBMI was the strongest non-conventional correlate of segmental body fat in total, male and female SPs. WTR and CI followed NBMI in men while WTR and WCR held the next highest ranks of correlations in total population as well as in women. Higher WCR in both sexes was more strongly correlated with visceral fat and lower appendicular than with truncal fat. Again, NBMI and BMI were comparably correlated with segmental fatness.

Altogether, WHtR, WHR, WC, BMI, and new BMI all were strong correlates of total, visceral and truncal adiposity in the entire population. Although adjustments for calf or thigh perimeters reduced the strength of associations between WC and measures of total, truncal and visceral fatness, these relationships remained strong. Thus, WC and BMI can be good indicators of fatness in healthy adults; however, they cannot differentiate fat depots accurately. In contrast, ABSI was not strongly related to any measure of fatness.

Table 4.3. Conventional anthropometric measures and fatness

Total and regional fatness		Conventional anthropometric measures							
		BMI	NC	AC	WC	TC	CC	WHR	WHtR
Male	%BF	0.70***	0.19	0.30	0.73***	0.11	0.39	0.80***	0.79**
	$\%BF_{ADP}$	0.76***	0.32	0.44*	0.72***	0.18	0.45*	0.72***	0.71***
	FM	0.81***	0.36	0.44*	0.84***	0.13	0.56**	0.88***	0.83***
	FM_{ADP}	0.81***	0.46*	0.60**	0.83***	0.17	0.59**	0.78***	0.74***
	VFA (cm^2)	0.79***	0.43	0.38	0.84***	0.08	0.48*	0.90***	0.84***
	TFM (kg)	0.79***	0.49*	0.50*	0.83***	0.01	0.70***	0.82***	0.74***
	AFM (kg)	0.92***	0.58*	0.66*	0.83**	0.17	0.66**	0.83**	0.72**
	UFM (kg)	0.86***	0.55*	0.63**	0.83***	0.14	0.74***	0.81***	0.73***
	LFM (kg)	0.93***	0.58*	0.67**	0.80***	0.22	0.64**	0.83***	0.70**
Female	% BF	0.81***	0.40*	0.68***	0.60**	0.30	0.29	0.64**	0.63***
	% BF_{ADP}	0.77***	0.08	0.28	0.34	0.20	0.30	0.23	0.45*
	FM	0.91***	0.51*	0.80***	0.75***	0.30	0.42*	0.69**	0.73***
	FM_{ADP}	0.81***	0.17	0.38	0.51*	0.31	0.49*	0.32	0.54**
	VFA (cm^2)	0.90***	0.53**	0.83***	0.77***	0.16	0.27	0.77**	0.79***
	TFM (kg)	0.72***	0.27	0.47	0.53*	0.06	0.21	0.49*	0.42
	AFM (kg)	0.92***	0.49*	0.67**	0.81***	0.32	0.43*	0.58**	0.73**
	UFM (kg)	0.90***	0.40	0.58*	0.67*	0.24	0.31	0.54*	0.62*
	LFM (kg)	0.92***	0.46*	0.65***	0.79***	0.32	0.42	0.55*	0.70***
Total	%BF	0.42**-	-0.01	0.21	0.32*	0.10	0.15	0.48**	0.50***
	$\%BF_{ADP}$	0.37*	-0.01	0.15	0.29*	0.11	0.21	0.29	0.43**
	FM	0.73***	0.38	0.54	0.69***	0.23	0.49***	0.70***	0.76***
	FM_{ADP}	0.68***	0.37	0.50	0.66***	0.27	0.56***	0.53***	0.68***
	VFA (cm^2)	0.75***	0.50***	0.58***	0.77***	0.18	0.46**	0.77***	0.82***
	TFM (kg)	0.68***	0.48**	0.54***	0.72***	0.12	0.55***	0.64***	0.66***
	AFM (kg)	0.33*	-0.01	0.19	0.25	0.07	0.18	0.34*	0.36*
	UFM (kg)	0.62***	0.32	0.47**	0.56**	0.18	0.44*	0.56***	0.60**
	LFM (kg)	0.22	-0.11	0.10	0.13	0.05	0.08	0.25	0.26

*Values are presented as r. For all correlations in male, female, and total participants, n=22, 28, and 50, respectively. *p<0.05; **p<0.01; ***p<0.001*

BMI: body mass index; NC: neck circumference; AC: arm circumference; WC: waist circumference; TC: thigh circumference; CC: calf circumference; WHR: waist to hip ratio; WHtR: waist to height ratio; BF: body fat; FM: fat mass; VFA: visceral fat area; TFM: trunk fat mass; AFM: appendicular fat mass; UFM: upper limb fat mass; LFM: lower limb fat mass.

Table 4.4. Non-conventional anthropometric measures and fatness

	Total and regional body fat	Non-conventional anthropometric measures					
		NBMI	WTR	WCR	NHtR	CI	ABSI
Male	%BF	0.74^{***}	0.61^{**}	0.56^{*}	0.40	0.58^{*}	0.64^{**}
	$\%BF_{ADP}$	0.76^{***}	0.57^{*}	0.55^{*}	0.44^{*}	0.57^{*}	0.48^{*}
	FM	0.81^{***}	0.70^{**}	0.58^{**}	0.50^{*}	0.64^{*}	0.54^{*}
	FM_{ADP}	0.77^{***}	0.67^{**}	0.57^{**}	0.49^{*}	0.64^{**}	0.37
	VFA (cm^2)	0.81^{***}	0.72^{***}	0.64^{**}	0.59^{**}	0.67^{**}	0.60^{**}
	TFM (kg)	0.76^{***}	0.75^{**}	0.49^{*}	0.51^{*}	0.65^{**}	0.35
	AFM (kg)	0.89^{***}	0.68^{*}	0.51^{*}	0.57^{*}	0.59^{*}	0.25
	UFM (kg)	0.82^{***}	0.63^{**}	0.46^{*}	0.58^{*}	0.55^{*}	0.23
	LFM (kg)	0.90^{***}	0.70^{**}	0.50^{*}	0.57^{*}	0.59^{**}	0.30
Female	% BF	0.81^{***}	0.39^{*}	0.48^{**}	0.46^{*}	0.22	0.14
	$\%BF_{ADP}$	0.77^{***}	0.19	0.18	0.23	0.01	0.20
	FM	0.88^{***}	0.53^{**}	0.55^{**}	0.51^{*}	0.36	0.13
	FM_{ADP}	0.77^{***}	0.28	0.24	0.22	0.19	0.15
	VFA (cm^2)	0.89^{***}	0.65^{***}	0.68^{***}	0.57^{**}	0.44^{*}	0.29
	TFM (kg)	0.63^{**}	0.48^{*}	0.46^{*}	0.14	0.34	-0.09
	AFM (kg)	0.87^{***}	0.57^{**}	0.61^{**}	0.41	0.50^{*}	0.09
	UFM (kg)	0.84^{***}	0.55^{**}	0.53^{*}	0.37	0.50^{*}	0.07
	LFM (kg)	0.88^{***}	0.48	0.60^{**}	0.37	0.37	0.08
Total	% BF	0.50^{***}	0.27	0.33^{*}	0.21	0.16	0.47^{**}
	$\%BF_{ADP}$	0.45^{**}	0.23	0.25	0.17	0.13	0.39^{**}
	FM	0.76^{***}	0.60^{**}	0.59^{***}	0.48^{***}	0.49^{**}	0.31^{*}
	FM_{ADP}	0.68^{***}	0.55^{**}	0.54^{***}	0.41^{**}	0.49^{**}	0.20
	VFA (cm^2)	0.76^{***}	0.71^{**}	0.71^{***}	0.60^{***}	0.61^{**}	0.35^{*}
	TFM (kg)	0.64^{***}	0.68^{**}	0.62^{***}	0.43^{**}	0.58^{**}	0.06
	AFM (kg)	0.39^{*}	0.22	0.20	0.14	0.12	0.29
	UFM (kg)	0.64^{***}	0.49^{**}	0.49^{**}	0.39^{*}	0.38^{*}	0.19
	LFM (kg)	0.29^{*}	0.11	0.12	0.04	0.02	0.29^{*}

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

NBMI: new BMI; WTR: waist to thigh ratio; WCR: calf to waist ratio; NHtR: neck to height ratio; CI: conicity index; ABSI: a body shape index. BF: body fat; FM: fat mass; VFA: visceral fat area; TFM: trunk fat mass; AFM: appendicular fat mass; UFM: upper limb fat mass; LFM: lower limb fat mass.

4.5 Height-adjusted leanness indices and anthropometric measures

When BIA-estimated measures of leanness/muscularity were adjusted by height to control for the influence of stature on the variability in lean compartments (Table 4.5), all indices except SMI showed stronger relationships with AC, BMI, NC and WC than with other conventional anthropometric measures in total SPs (Table 4.5). AC was the strongest correlate of FFMI; BMI was the strongest correlate of TSMI and LSMI while NC was the strongest correlate of $FFMI_{ADP}$ in total SPs. USMI correlated equally with AC, BMI, and NC. In male SPs, significant correlations were as follows: FFMI with AC and TC; SMI with WHtR, WHR, WC and BMI; USMI and LSMI with NC and ASMI with AC, BMI, and TC. In female SPs, only SMI and $FFMI_{ADP}$ correlated significantly with the conventional anthropometric measures, most strongly with BMI and WC. SMI demonstrated consistently negative relationships with all anthropometric measures in both sexes.

Among the non-conventional anthropometric measures (Table 4.6), NBMI was the strongest non-conventional correlate of height-adjusted leanness indices in total SPs, most strongly with TSMI, followed by NHtR. ABSI also showed negative relationships with all leanness indices but ASMI. NHtR was the strongest non-conventional anthropometric correlate of SMI.

Overall, AC and NC were found to be the strongest anthropometric indicators of stature-normalised total leanness and muscularity in the entire population. BMI and new BMI were the strongest correlates of truncal muscularity whilst AC, NC, BMI and WC were comparably strong indicators of appendicular muscularity. Again, ABSI was the only negative correlate of leanness/muscularity in total population. The magnitude of associations was, however, lower than the figure observed for stature-unadjusted leanness/muscularity measures These observations lend support to the previous notion that the measures widely known as the markers of fatness may be influenced by changes in the lean compartments too. Also, correlation of anthropometric and BIA-estimated measures cannot be attributed to the variations in height.

Table 4.5. Conventional anthropometric measures and height-adjusted leanness

	Height-adjusted leanness indices (kg/m^2)	**Conventional anthropometric measures**							
		BMI	NC	AC	WC	TC	CC	WHR	WHtR
Male	FFMI	0.39	0.41	0.67**	0.12	0.48*	0.33	0.12	-0.01
	$FFMI_{ADP}$	0.28	0.35	0.35	0.15	0.16	0.13	0.23	0.13
	SMI	0.38	0.46*	0.68***	0.10	0.46*	0.37	0.10	-0.04
	TSMI	0.46*	0.46*	0.73***	0.49*	0.59*	0.34	0.58**	0.46
	ASMI	0.55*	0.20	0.61**	0.26	0.54*	0.32	0.27	0.20
	USMI	0.32	0.60**	0.59**	0.21	0.45	0.16	0.24	0.15
	LSMI	0.18	0.52*	0.52*	0.32	0.39	0.31	0.32	0.31
Female	FFMI	0.30	0.28	0.55*	0.20	0.01	0.02	0.26	0.18
	$FFMI_{ADP}$	0.51*	0.27	0.47	0.35	0.41*	0.24	0.15	0.40*
	SMI	0.08	0.31	0.15	-0.02	-0.22	-0.22	0.09	0.09
	TSMI	-0.14	-0.03	0.04	0.04	0.09	-0.07	-0.07	0.22
	ASMI	0.02	-0.19	-0.28	-0.16	-0.07	-0.15	-0.18	-0.03
	USMI	-0.16	-0.11	-0.09	-0.08	-0.04	0.01	0.01	0.05
	LSMI	-0.29	-0.20	-0.31	-0.31	-0.14	-0.12	-0.12	-0.10
Total	FFMI	0.59**	0.67**	0.76***	0.53***	0.36*	0.46*	0.40*	0.34*
	$FFMI_{ADP}$	0.61***	0.63***	0.59***	0.58***	0.42**	0.47***	0.40*	0.47**
	SMI	0.47***	0.63***	0.59***	0.41**	0.21	0.32*	0.31*	0.28*
	TSMI	0.68**	0.53**	0.58**	0.56**	0.41*	0.38*	0.38	0.51**
	ASMI	0.60***	0.61***	0.57***	0.57***	0.35*	0.46*	0.35	0.42*
	USMI	0.58***	0.57***	0.57**	0.51***	0.34*	0.37*	0.37*	0.39*
	LSMI	0.50**	0.41*	0.42**	0.39**	0.22	0.25	0.27	0.34*

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

BMI: body mass index; NC: neck circumference; AC: arm circumference; WC: waist circumference; TC: thigh circumference; CC: calf circumference; WHR: waist to hip ratio; WHtR: waist to height ratio; FFMI: fat-free mass index; SMI: skeletal muscle index; TSMI: truncal skeletal muscle index; ASMI: appendicular skeletal muscle index; USMI: upper limb skeletal muscle index; LSMI: lower limb skeletal muscle index.

Table 4.6. Non-conventional anthropometric measures and height-adjusted leanness

Height-adjusted leanness indices (kg/m^2)		**Non-conventional anthropometric measures**					
		NBMI	WTR	WCR	NHtR	CI	ABSI
Male	FFMI	0.31	-0.10	-0.04	0.21	-0.12	-0.49*
	$FFMI_{ADP}$	0.36	0.07	0.08	0.28	-0.06	-0.10
	SMI	0.30	-0.11	-0.08	0.25	-0.15	-0.53*
	TSMI	0.69**	0.19	0.36	0.52*	0.16	0.05
	ASMI	0.53*	0.68*	0.10	0.57*	0.59*	0.25
	USMI	0.40	0.01	0.14	0.26	-0.03	-0.19
	LSMI	0.56**	0.11	0.16	0.24	0.05	0.03
Female	FFMI	0.28	0.19	0.20	0.26	0.03	-0.09
	$FFMI_{ADP}$	0.40	0.08	0.22	0.24	0.06	-0.20
	SMI	0.13	0.12	0.12	0.46*	-0.12	0.20
	TSMI	0.39	-0.05	0.12	0.10	-0.22	0.22
	ASMI	0.07	-0.13	-0.09	-0.02	-0.26	0.12
	USMI	0.18	-0.09	0.01	0.02	-0.25	0.13
	LSMI	0.09	-0.23	-0.09	-0.03	-0.46*	0.15
Total	FFMI	0.49**	0.38*	0.38*	0.49*	0.37*	-0.43**
	$FFMI_{ADP}$	0.55***	0.41*	0.43**	0.54***	0.45**	-0.16
	SMI	0.41**	0.33*	0.31*	0.56***	0.26	-0.28
	TSMI	0.65**	0.38*	0.47**	0.51*	0.35*	-0.09
	ASMI	0.52**	0.22	0.42**	0.14	0.12	0.29
	USMI	0.50**	0.37*	0.41**	0.45**	0.35*	-0.26
	LSMI	0.47**	0.30*	0.32*	0.37*	0.23	-0.13

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

NBMI: new BMI; WTR: waist to thigh ratio; WCR: waist to calf ratio; NHtR: neck to height ratio; CI: conicity index; ABSI: a body shape index; FFMI: fat-free mass index; SMI: skeletal muscle index; TSMI: truncal skeletal muscle index; ASMI: appendicular skeletal muscle index; USMI: upper limb skeletal muscle index; LSMI: lower limb skeletal muscle index.

4.6 Height-adjusted fatness indices and anthropometric measures

In total population (Table 4.7), WHtR and BMI displayed the highest level of correlation with height-adjusted total, truncal and upper limb fatness, followed by WHR and WC. No significant relationship was found for the appendicular and lower limb fat indices. WHtR, BMI and WC were equally correlated with TFMI. For FMI and UFMI, BMI and WHtR were respectively the strongest correlates. In men, WHR exhibited the strongest correlations with all indices, with LFMI being the most closely related index, followed by FMI and UFMI. For all fatness indices, relationships were stronger in male than in female SPs. In women, BMI showed the closest relationships with height-adjusted total and segmental body fat. WHtR and WC were almost equally correlated with the appendicular fat indices. TC did not show any significant relationship with the height-adjusted body fat indices in total, male or female SPs.

In men and women, NBMI was the strongest non-conventional anthropometric correlate of all height-adjusted fat indices (Table 4.8).

Thus, for a given height, new BMI, BMI and WHtR appear to be stronger indicators of total and upper limb fatness in otherwise healthy adults as compared to WC and WHR. In contrast, all four anthropometric measures demonstrate equally strong correlations with truncal fatness. It is noteworthy that none of these measures related significantly to lower limb fatness. Instead, WTR, NHtR, conicity index and ABSI correlate significantly to lower appendicular adiposity and may be used as surrogate measures of this fat compartment.

Table 4.7. Conventional anthropometric measures and height-adjusted fatness

	Height-adjusted fatness indices (kg/m^2)	Conventional anthropometric measures							
		BMI	NC	AC	WC	TC	CC	WHR	WHtR
Male	FMI	0.80^{***}	0.45^{*}	0.52^{*}	0.81^{**}	0.18	0.65^{**}	0.87^{**}	0.78^{*}
	FMI_{ADP}	0.78^{***}	0.40	0.56^{*}	0.83^{***}	0.20	0.51^{*}	0.83^{***}	0.80^{***}
	TFMI	0.73^{**}	0.40	0.42	0.78^{**}	0.02	0.61^{**}	0.80^{**}	0.74^{**}
	AFMI	0.80^{**}	0.45	0.59^{*}	0.73^{*}	0.33	0.59^{**}	0.82^{*}	0.70^{*}
	UFMI	0.85^{***}	0.49^{*}	0.58^{*}	0.83^{***}	0.18	0.65^{**}	0.86^{***}	0.80^{***}
	LFMI	0.85^{***}	0.53^{*}	0.63^{**}	0.81^{***}	0.26	0.57^{*}	0.89^{***}	0.77^{**}
Female	FMI	0.83^{**}	0.33	0.57	0.69^{**}	0.13	0.25	0.53^{*}	0.65^{*}
	FMI_{ADP}	0.67^{**}	0.09	0.36	0.45^{*}	0.29	0.38^{*}	0.30	0.57^{*}
	TFMI	0.61^{*}	0.29	0.53^{*}	0.60^{**}	0.13	0.26	0.51^{*}	0.53^{*}
	AFMI	0.79^{*}	0.42^{*}	0.61^{*}	0.75^{***}	0.31	0.37	0.50	0.74^{*}
	UFMI	0.75^{*}	0.34	0.57	0.63^{*}	0.23	0.24	0.52^{*}	0.65^{*}
	LFMI	0.85^{***}	0.40^{*}	0.65^{***}	0.76^{***}	0.33	0.35	0.55^{*}	0.78^{***}
Total	FMI	0.65^{***}	0.16	0.33^{*}	0.47^{**}	0.10	0.31	0.51^{**}	0.57^{**}
	FMI_{ADP}	0.61^{***}	0.20	0.38^{*}	0.53^{***}	0.23	0.40^{**}	0.47^{**}	0.65^{***}
	TFMI	0.67^{***}	0.40^{**}	0.50^{***}	0.67^{***}	0.14	0.49^{*}	0.63^{***}	0.67^{***}
	AFMI	0.25	-0.12	0.09	0.13	0.10	0.08	0.24	0.30
	UFMI	0.53^{**}	0.14	0.33^{*}	0.41^{*}	0.14	0.27	0.48^{**}	0.55^{**}
	LFMI	0.14	-0.24	-0.01	0.01	0.01	-0.05	0.17	0.21

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

BMI: body mass index; NC: neck circumference; AC: arm circumference; WC: waist circumference; TC: thigh circumference; CC: calf circumference; WHR: waist to hip ratio; WHtR: waist to height ratio; FMI: fat mass index; TFMI: truncal fat mass index; AFMI: appendicular fat mass index; UFMI: upper limb fat mass index; LFMI: lower limb fat mass index.

Table 4.8. Non-conventional anthropometric measures and height-adjusted fatness indices

Height-adjusted fatness indices		Non-conventional anthropometric measures					
		NBMI	WTR	WCR	NHtR	CI	ABSI
Male	FMI	0.82***	0.65**	0.61**	0.55*	0.57*	0.41
	FMI_{ADP}	0.77***	0.65**	0.63**	0.54*	0.62**	0.51*
	TFMI	0.71**	0.68*	0.50*	0.61**	0.57*	0.45
	AFMI	0.79**	0.62**	0.45	0.63**	0.54*	0.38
	UFMI	0.84***	0.58**	0.51*	0.29	0.41*	0.11
	LFMI	0.83***	0.24	0.56*	0.25	0.10	0.29
Female	FMI	0.81**	0.44	0.52**	0.40	0.27	0.20
	FMI_{ADP}	0.69**	0.52**	0.25	0.44*	0.40*	0.25
	TFMI	0.56*	0.65**	0.51*	0.55*	0.57*	0.41
	AFMI	0.75*	0.65**	0.59**	0.54*	0.62**	0.51*
	UFMI	0.73**	0.68*	0.53*	0.61**	0.57*	0.45
	LFMI	0.82***	0.62**	0.61**	0.63**	0.54*	0.38
Total	FMI	0.71***	0.43**	0.48***	0.28	0.31*	0.31
	FMI_{ADP}	0.67***	0.43**	0.42**	0.36*	0.34*	0.39*
	TFMI	0.66***	0.35	0.54**	0.32*	0.22	0.35*
	AFMI	0.34*	0.08	0.12	0.08	0.01	0.36*
	UFMI	0.60***	0.43**	0.34*	0.28	0.31*	0.31
	LFMI	0.25	0.43**	0.05	0.36*	0.34*	0.39*

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

NBMI: new BMI; WTR: waist to thigh ratio; WCR: waist to calf ratio; NHtR: neck to height ratio; CI: conicity index; ABSI: a body shape index; FFMI: fat-free mass index; FMI: fat mass index; TFMI: truncal fat mass index; AFMI: appendicular fat mass index; UFMI: upper limb fat mass index; LFMI: lower limb fat mass index

Discussion

This is the first study that comprehensively explores the relationships between conventional and non-conventional anthropometric measures with absolute and height-normalised parameters of total and segmental leanness and fatness in free-living healthy adults.

In the entire study population, NC and AC were found to be the closest conventional anthropometric correlates of total FFM as well as total and segmental skeletal muscle mass followed by WC, BMI and CC whilst ABSI was the only strong but negative correlate of these parameters. The absolute effect size of ABSI was comparable to AC for total parameters but it was inferior to NC, AC, BMI and WC for segmental parameters. Of note, the strength of association of all anthropometric measures was slightly greater for total and truncal than appendicular parameters of lean mass. Also, the adjustment of FFM as well as total and segmental skeletal muscle mass for height weakened change their relationship with anthropometric measurements but did not substantially altered the pattern of these associations except for ABSI which was no longer a significant correlate of segmental muscle mass. AC has been suggested as a reliable measure of muscle mass in the evaluation of sarcopenia and nutritional status across different groups of population (Al-Gindan *et al.*, 2014). As compared to BMI and CC, AC has also been shown to be a stronger negative predictor of long-term survival in the elderly (Wijnhoven *et al.*, 2010); however, it cannot be overemphasised that upper arm circumference is anatomically related to bone, skeletal muscle and subcutaneous adipose tissue. For this reason, like other limb circumferences, the association of AC with health outcomes may stem from changes in the quality and quantity of these three tissues. Another interesting observation was that TC, WHR and WHtR exhibited similar trend of relationship with BIA-derived measures of leanness. These anthropometric indices were more strongly related to FFM and upper body skeletal muscle mass than total skeletal muscle mass and leg muscle content (the main metabolic constituent of the musculature), suggesting that mid-thigh circumference may be reflect subcutaneous fat tissue better than muscle tissue in adults with less muscular body built.. The established independent and oppositely directed link between insulin sensitivity and waist versus thigh and hip circumference in men and women (Snijder *et al.*, 2003) lends more support to the view that improved metabolic profile of individuals with

larger thighs and hips can be due to the more favourable metabolism of their subcutaneous adipocytes (Van Pelt *et al.*, 2002). Of particular interest was the relationship of NC and WC with total and regional muscularity as well as total leanness which indicates these anthropometric measures may not exclusively reflect the adiposity status of healthy adults and their role as the predictors or indicators of altered metabolic processes can be ascribed to the underlying adaptive and maladaptive changes in fat and fat-free components of body composition. Notably, when the contribution of BMI to WC was discounted by creating ABSI, the direction of association between waist circumference and leanness/muscularity was reversed. This was opposite to the observed association between CI, another body size adjusted index of WC, and BIA-estimated FFM and skeletal muscle mass. Hence, ABSI discloses depleted lean mass better than CI as it indicates the residual WC after controlling for body mass and height. Therefore, individuals with high ABSI have a greater fraction of visceral fat and a smaller fraction of appendicular lean tissue at a given BMI and height. The inverse relationship between ABSI (as a measure of body shape) and lean tissue mass is supported by the findings from a secondary analysis of the NHANES 1999-2004 data (Krakauer and Krakauer, 2012). This study showed negative correlation between ABSI and DXA-estimated lower limb lean mass adjusted for height. Also, in a cross-sectional study of 200 Italian and Slovenian adults with elevated BMI, men and women with higher ABSI had significantly lower FFMI (Biolo *et al.*, 2015). Given the inverse association of total and appendicular muscle mass with physical disability, increased morbidity and mortality risk (Chang and Lin, 2016), ABSI may be used as a surrogate measure of reduced lean and muscle tissue to predict adverse outcomes in adults. This supports the hypothesis that the consistently observed link between general, upper-body, and abdominal adiposity (determined anthropometrically by BMI, NC, and WC) and metabolic abnormalities may also be influenced by concomitant changes in the quantity and regional distribution of lean mass.

In accord with this notion, Takai *et al.* reported that WHtR and body mass to WC ratio were independent predictors of DXA-measured FFM in Japanese male athletes (Takai *et al.*, 2018). Thus, the combined contribution of FM and FFM should be carefully considered when using BMI, NC, and WC in the assessment of a variety of clinical outcomes in otherwise healthy adults. Another noticeable observation was

that NC related to upper and lower-limb muscularity more strongly than AC and CC. MUAC and CC have been commonly applied as the proxy measures of lean or muscle mass in both observational and interventional studies but the potential role of NC as an indicator of appendicular muscularity has not been investigated so far. It is possible that neck circumference can be used as a measure of skeletal muscle content in both upper and lower extremities.

Overall, these observations indicate that at a given height, large arm and neck circumferences reflect higher total and segmental muscularity better than other anthropometric indices in otherwise healthy adults. Also, an increased ABSI can be an indicator of diminished leanness in this population. Nevertheless, the association of AC, CC and NC with total and segmental fatness should not be overlooked.

When stratified by sex, ABSI emerged as the strongest (yet negative) anthropometric correlate of total fat-free and muscle mass whilst AC was the strongest correlate of segmental muscle mass in men. The other significant indicators of total leanness and segmental muscularity were NC, CC (before height adjustment) and TC (after height adjustment) in male SPs. In contrast, significant relationships in female SPs were observed just between FFM_{ADP} and CC (directly) and FFM and ABSI (inversely). These were in contradiction to the significant correlations of all non-conventional anthropometric measures with the above parameters observed before sex-stratification of data. The observed discrepancy between total and sex-stratified correlations can be explained by the amalgamation paradox (Berman *et al.*, 2012). This happens when two groups with contrasting patterns of binary associations between pairs of variables are aggregated. In this case, the overlap between data-pairs pertinent to each group improves the linearity of the combined group, distorting the actual relationships. The lack of significant relationships in female SPs may be due to their lower total and regional skeletal muscle mass and the higher proportion of subcutaneous fat in their trunk and extremities. As a result, anthropometric measurements in women may reflect total and segmental fat mass rather than muscle mass (Kyle *et al.*, 2001). When the effect of body size is controlled (as in NBMI and ABSI), the contribution of non-muscle compartments to the anthropometric indices is attenuated and the direction of association is reversed.

A more plausible explanation could be the established limitation of subgroup analysis. Although it was attempted to improve the statistical power of sex-stratified analyses of the study population by having relatively equal proportions of male and female SPs and testing anthropometric and body composition variables along their continuum, the lack of prior probability estimation and sample size calculation based on the main effects in the entire population would result in an inadequate power and subsequently higher probability of false negative findings from the subgroup analysis (Burke *et al.*, 2015).

With respect to total and segmental fatness, WHtR, NBMI, WHR, BMI, WTR, WC and WCR were found to be strong indicators of total, visceral and truncal fatness in the entire population, with the relationships being stronger for visceral adiposity whereas ABSI represented visceral but not total or truncal adiposity. This is not unexpected as ABSI has been proposed to control for the dependence of WC on height and BMI. In this regard, an analysis of the NHANES 1999–2004 data (Krakauer and Krakauer, 2012), showed that WC was weakly correlated with DXA-measured Z score of trunk fat mass adjusted for body size. When the influence of body size is discounted, the association of WC and subcutaneous fat depot (the main adipose constituent of trunk and limbs) loses significance. What remains is the association between the body shape (the component of WC which reflects central distribution of body mass) and visceral fat depot. The significant associations of WHtR, WC and WHR with CT-determined total and visceral fat areas have been established (Ashwell, Cole and Dixon, 1985, 1996; Seidell *et al.*, 1987; Busetto *et al.*, 1992).

The effect size of these measures on appendicular (especially lower limb) fatness was smaller. In fact, NBMI and ABSI were the only indices which showed significant albeit weak relationship with the fat content of lower limbs. This observation demonstrates that the anthropometric measurements are not useful surrogates for the lower-body adiposity and should be interpreted carefully when used as the proxy measures of appendicular adiposity. In addition, their comparably close relationship with total, visceral and truncal adiposity suggests that these measures cannot differentiate between subcutaneous and visceral fat depots. Interestingly, NC and AC were related to visceral and truncal but not total fat mass, indicating that neck and arm perimeters reflect upper body rather than general

adiposity. Thus, the total and segmental quantity of lean tissues as well as the amount of fat stored in the truncal region of adults are jointly linked to the circumference of neck and arms. This is in contrast to previous reports on the strong associations between NC, visceral and subcutaneous adipose tissue (Sjöström *et al.*, 1995; Yang *et al.*, 2010; Aswathappa *et al.*, 2013). Nevertheless, these studies had been mainly conducted on obese or insulin resistant subjects. In this context, the established link between increased NC and metabolic risk factors (Ben-Noun and Laor, 2006), OSA (Katz *et al.*, 1990) or polycystic ovary syndrome (Dixon and O'brien, 2002) may not be solely due to the excessive upper-body fatness. The influence of lean tissues on neck circumference may be an explanation for the superior performance of NC in predicting metabolic syndrome and obstructive sleep apnoea in comparison to WC or BMI, especially in men (Pływaczewski *et al.*, 2008; Onat *et al.*, 2009).

The finding of positive correlation of AC and (less strongly) CC with absolute as well as height-normalised total and segmental adiposity in the present research suggests that the frequently observed association between low CC or AC and unfavourable health outcomes, including lower quality of life and higher mortality in different groups of population (Powell-Tuck and Hennessy, 2003; Mason, Craig and Katzmarzyk, 2008; Flegal and Graubard, 2009), may be due to concomitant loss of fat and muscle mass (Cesari *et al.*, 2009; Huang *et al.*, 2010). However, the lack of significant relationships between CC and absolute or height-adjusted measures of leanness in the current study in both sexes shows that the negative impact of low calf and arm circumferences on health outcomes is mostly attributable to the loss of fat rather than muscle, at least in the non-elderly healthy population.

In contrast, TC was not significantly related to any fat component. Given the significant relationship between thigh circumference and total as well as segmental muscle mass in the entire population of the current study, it can be inferred that the perimeter of mid-thigh area is not indicative of total or segmental body fatness in healthy adults. This is conflict with the findings of Snijder *et al.* (Snijder *et al.*, 2005) who showed significant association of mid-thigh circumference with CT-measured thigh total fat area and muscle area. That study, however, was conducted on well-functioning adults aged 70-79 years. BIA-related estimation error of fat

components especially in lean individuals may also be a reason for the observed dissociation of TC and fatness in the present study.

Akin to the associations between anthropometric indices and measures of leanness, stature adjustment of total and regional body fat attenuated but did not change the pattern of associations with anthropometric measures, denoting the ability of these parameters to represent total and segmental leanness and adiposity.

Close associations of WHtR, NBMI, WHR, BMI, WTR, WC and WCR with total and segmental adiposity were reproduced in male SPs whereas BMI, NBMI, WC and WHtR emerged as the strong indicators of total and regional fatness in female SPs. Interestingly, AC and CC indicated truncal and appendicular adiposity better than total and visceral adiposity ascompared to total and visceral fatness in males. In contrast, AC was a better indicator of total and visceral fatness in female SPs. Sexual disparity was also found for NC-fatness relationship. While neck circumference reflected non-visceral segmental adiposity in men, it had significant relationship with appendicular and visceral adiposity in women. In addition, ABSI and CI represented total and segmental fatness more consistently in men. They were only related to visceral fatness in women. These observations indicate a sex-specific relationship between anthropometric indices and body composition due to the differential proportion and distribution of fat and fat-free compartments in male and female adults (Karastergiou *et al.*, 2012; Siervo *et al.*, 2015). These differences can be explained by the fact that, adjusted for height, men have higher lean mass, greater arm and leg muscle mass, lower total fat mass, centrally accumulated adipose tissue, and less appendicular fat. On the contrary, women tend to have higher total fat and peripherally distributed adipose tissue (WHO, 2011). Moreover, geometric properties as well as soft tissue composition of neck, arms and legs play important parts in the sexual dimorphism in the associations of anthropometric measures and other clinical outcomes even among height-matched individuals (Antoszewska and Wolański, 1992; Vasavada, Danaraj and Siegmund, 2008). Nevertheless, inadequate power of the present study for subgroup analysis limits the accuracy of these results.

Collectively, these findings suggest that both conventional and non-conventional anthropometric indices except TC and ABSI represent total, central and peripheral adiposity in male and female adults. Additionally, BMI (and/or NBMI), WHtR,

WHR and WC are comparably strong surrogates of total and segmental fatness in healthy adults. On the contrary, most of the anthropometric measures cannot be relied upon as the pure indicators of leanness, although ABSI, neck circumference and arm circumference are better indicators of total and segmental muscularity status.

However, it should be remembered that these relationships were not adjusted for age, total quantity of fat and fat-free compartments and categories of relative body composition. Moreover, it is well-known that anthropometric measurements are subject to several limitations. They poorly distinguish between visceral and subcutaneous fat depots, fail to discriminate segmental lean and fat tissues, and are unable to make differences between muscle, bone and other components of fat-free mass. Repeatability and reproducibility of these measurements are not optimal. There is considerable intra and inter-observer variation in the recorded readings. Biological factors, including bony structure, hydration and prandial states, phases of respiration, posture, together with laxity of muscles and skin also influence the accuracy and precision of anthropometric measurements. Variability in anatomical landmarks and techniques of measurement may be other sources of error. Besides, age, sex, and ethnicity-specific alterations in body composition complicates the harmonised interpretation of the values. When absolute measurements are composited into ratios or indices, the propagation of error increases. Further, the combination of measurements would inevitably lead to the loss of information, causing some uncertainty about the underlying changes in fat or fat-free components. Notwithstanding these drawbacks, anthropometry is a valuable assessment tool in clinical setting because of reasonably low cost, participant burden, practitioner burden of data collection and analysis, information bias, and cognitive capacity as well as favourably high availability, practicality and inclusivity (MRC epidemiology unit, 2016). The estimation error inherent in the measurement of fat and lean compartments by BIA might have also confounded the actual relationships. Nevertheless, as discussed thoroughly in chapter 2, direct segmental multifrequency assessment of body composition using the In-Body and Tanita analysers has been shown to have good agreement to DXA in the quantification of total FFM, FM and %BF as well as truncal and appendicular lean mass in otherwise healthy adults(Ling *et al.*, 2011; Verney *et al.*, 2015)

Chapter 5

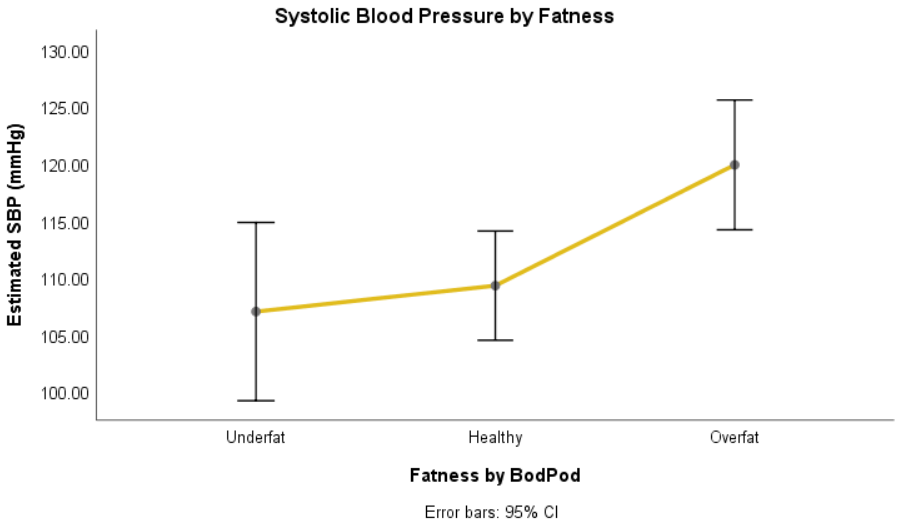
Body Composition and Blood Pressure

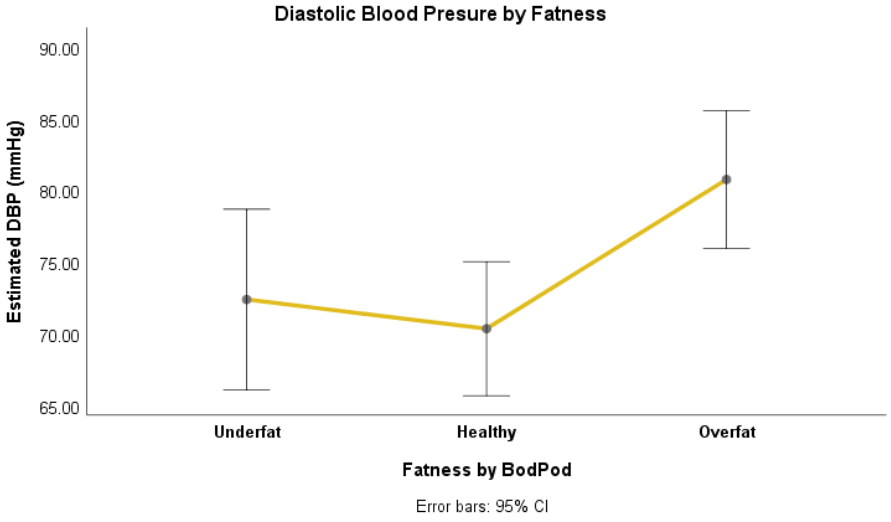
SPs were divided into three groups of fatness, namely underfat, healthy-range and overfat/obese based on the BMI, age, sex, and ethnicity-specific body fat ranges recommended by Gallagher *et al.* (Gallagher *et al.*, 2000). The effect of fatness status on the measures of systemic blood pressure (SBP, DBP and MAP) was analysed using univariate ANOVA with the Bonferroni-adjusted post-hoc test. Pearson's correlation test was conducted to examine the relationship between measures of systemic BP and total as well as segmental fatness and leanness. Correlations were additionally stratified by sex. Sex-specific tertiles of total and regional relative boy composition were created and compared in relation to indices of BP by ANOVA with post-hoc analysis using Tukey's HSD test. FM/FFM and TFM/ASM as the whole-body and segmental indicators of metabolic load-capacity balance were included in the linear regression models with heteroscedasticity-consistent standard errors. Models were also adjusted for age, sex and ethnicity.

Results

5.1 Fatness and systemic blood pressure

Fatness status had a significant effect of on SBP ($F(2,47)=5.31$, $p=.007$, $\eta_p^2=.18$), DBP ($F(2,47)=5.26$, $p=.009$, $\eta_p^2=.18$), and MAP $F(2,47)=6.60$, $p=.003$, $\eta_p^2=.22$). Thus, fatness status explained 18% of SBP and DBP total variance and 22% of MAP total variance among SPs. Pairwise comparisons indicated that SBP in overfat SPs was significantly higher than underfat (*MD*=12.86mmHg, $p=.031$) and normal-fat (*MD*=10.59mmHg, $p=.020$) SPs. Overfat SPs also had higher DBP than their underfat (*MD*=8.35, $p=.12$) and normal-fat (*MD*=10.38, $p=.009$) counterparts. Similarly, MAP was higher in overfat than underfat (*MD*=8.20, $p=.10$) and normal-fat (*MD*=10.80, $p=.003$) SPs (Figure 5.1).





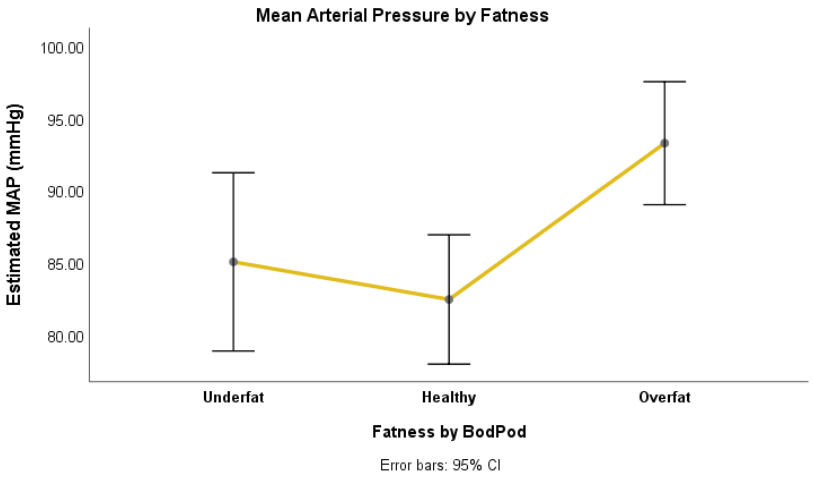


Figure 5.1 Fatness and systemic blood pressure; a) Systolic, b) Diastolic, c) Mean Arterial Pressure.

5.2 Total and segmental body composition and systemic blood pressure

In the entire study population, total and segmental skeletal muscle mass correlated significantly with SBP and PP (Table 5.1). Additionally, DBP correlated negatively but non-significantly with total and segmental skeletal muscle mass. Notably, the magnitude of relationship between total quantity of skeletal muscle and parameters of systemic BP was comparable to that of truncal and appendicular muscle mass. None of the skeletal muscle compartments correlated with mean arterial pressure.

This may indicate a greater influence of general and regional muscularity on systolic rather than diastolic pressure; therefore, otherwise healthy individuals with larger quantity of skeletal muscle may have higher SBP and slightly lower DBP, and consequently wider pulse pressure as compared to their less muscular counterparts.

In contrast, total, truncal and appendicular fat mass showed comparably significant relationships with DBP and MAP in the entire population. In addition, total and truncal fat mass correlated significantly with SBP. All segmental fat compartments showed negative but non-significant associations with pulse pressure. The only observed significant correlation was between UFM and PP in total population. As a result, in free-living healthy adults, general and central adiposity relate positively to systolic and diastolic BP, with slightly greater influence on the diastolic component. In comparison, peripheral adiposity is mostly related to the diastolic component of systemic BP. It does not, however, seem that fat component (except upper-limb fat compartment) of body composition could be a major correlate of pulse pressure.

In the entire population, SBP and PP had stronger relationships with muscular compartments than adipose compartments, whereas DBP and MAP correlated more strongly with adiposity than with muscularity.

Table 5.1. Lean composition and blood pressure

	Blood pressure (mmHg)	Lean compartment					Fat compartment				
		FFM	TSM	ASM	USM	LSM	FM	TFM	AFM	UFM	LFM
Male	**SBP**	0.13	0.17	0.07	0.09	0.07	0.49*	0.45*	0.50*	0.41	0.54*
	DBP	-0.30	-0.27	-0.31	-0.32	-0.35	0.55*	0.56*	0.51*	0.46*	0.52*
	MAP	-0.18	-0.15	-0.20	-0.20	-0.23	0.58**	0.58**	0.56*	0.49*	0.57*
	PP	0.50*	0.51*	0.44	0.48*	0.49*	-0.12	-0.17	-0.05	-0.10	-0.02
Female	**SBP**	-0.13	-0.08	-0.15	-0.05	-0.20	0.36	0.17	0.43	0.33	0.37
	DBP	-0.10	-0.06	-0.13	-0.06	-0.18	0.52*	0.37	0.52*	0.42	0.49
	MAP	-0.12	-0.07	-0.14	-0.06	-0.20	0.49*	0.32	0.52*	0.41	0.48
	PP	-0.06	-0.04	-0.05	0.01	-0.05	-0.15	-0.24	-0.07	-0.08	-0.11
Total	**SBP**	0.31*	0.32*	0.30*	0.33*	0.28	0.38*	0.38*	0.19	0.11	0.32
	DBP	-0.11	-0.10	-0.11	-0.11	-0.13	0.53***	0.45**	0.45**	0.41**	0.43*
	MAP	0.05	0.05	0.04	0.05	0.02	0.52***	0.46**	0.39*	0.33*	0.43*
	PP	0.52***	0.52***	0.51***	0.53***	0.52***	-0.11	-0.02	-0.27	-0.32*	-0.09

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

All compartments were measured by Tanita SEG-MF Bioelectrical Impedance Analyser.

FFM: fat-free mass; TSM: trunk skeletal muscle mass; ASM: appendicular skeletal muscle mass; USM: upper limb skeletal muscle mass; LSM: lower limb skeletal muscle mass TFM: trunk fat mass; AFM: appendicular fat mass; UFM: upper limb fat mass; LFM: lower limb fat mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure.

5.3 Body composition phenotypes and systemic blood pressure

To investigate the relative contribution of fatness and leanness to the parameters of systemic blood pressure, total, truncal and appendicular body composition phenotypes were created based on the tertiles of the corresponding fat and lean compartments.

Across sex-specific body composition phenotypes, only DBP and MAP were found to have significantly different mean values (Figures 5.2 and 5.3). For total body composition phenotypes, High-FM/High-FFM phenotype had significantly higher DBP than Low-FM/Mid-FFM (*MD*=23.25 mmHg, $p<0.05$) and Mid-FM/High FFM (*MD*=21.33 mmHg, $p<0.05$) phenotypes. With respect to MAP, the significant difference was observed between High-FM/High-FFM and Low-FM/Mid-FFM phenotypes (*MD*=22.81 mmHg, $p<0.05$). Consequently, healthy adults with the highest degrees of total fatness and leanness had at least 20mmHg higher diastolic and mean arterial pressures than those with the lowest levels of fatness and mid-range leanness. By contrast, DBP and MAP of individuals who had the lowest level of leanness did not differ significantly by their fatness status. This may imply that potentially harmful effects of general adiposity are exerted on diastolic and mean arterial pressure when the lean compartment is expanded. A similar trend was observed across truncal phenotypes where DBP was significantly higher in SPs with high truncal fat and high skeletal muscle mass than those with low fat but high skeletal muscle mass in truncal region (*MD*=23.98 mmHg, $p<0.05$) although MAP did not differ significantly between truncal phenotypes.

On the contrary, DBP rose steadily across levels of appendicular fat irrespective of the corresponding muscularity status. Nevertheless, the magnitude of effect exerted by the increased fat content of the limbs on diastolic pressure was greater when the concomitant muscle content was also increased. Among appendicular phenotypes, SPs with Low-AFM/High-ASM phenotype had significantly lower DBP than those with Mid-AFM/Low-ASM (*MD*=-16.72 mmHg, $p<0.05$), High-AFM/Mid-ASM (*MD*=-19.72 mmHg, $p<0.05$) and High-AFM/High-ASM (*MD*=-24.01 mmHg, $p<0.01$) phenotypes; DBP was also lower in Mid-AFM/High-ASM SPs than those with High-AFM/High-ASM phenotype (*MD*=-22.25 mmHg, $p<0.01$).

A comparable association was observed between MAP and appendicular body composition phenotypes where MAP was significantly lower in Low-AFM/High-ASM SPs than those with Mid-AFM/Low-ASM (*MD*=-16.66 mmHg, $p<0.05$), High-AFM/Mid-ASM (*MD*=-16.80 mmHg, $p<0.05$) and High-AFM/High-ASM (*MD*=-24.60 mmHg, $p<0.01$) phenotypes; SPs with Mid-AFM/High-ASM phenotype had also lower MAP than High-AFM/High-ASM SPs (*MD*=-21.83 mmHg, $p<0.01$).

Once again, the largest difference in the mean arterial pressure (approximately 25mmHg) was observed between adults with the lowest and highest appendicular fat mass only if both groups had high degrees of appendicular muscularity, reinforcing the possibility that the quantity of total and segmental skeletal muscle may augment the unfavourable influence of excessive adiposity on the diastolic component of systemic pressure.

Despite significant effects on DBP and MAP, total and segmental body composition phenotypes showed no significant association with systolic pressure or pulse pressure.

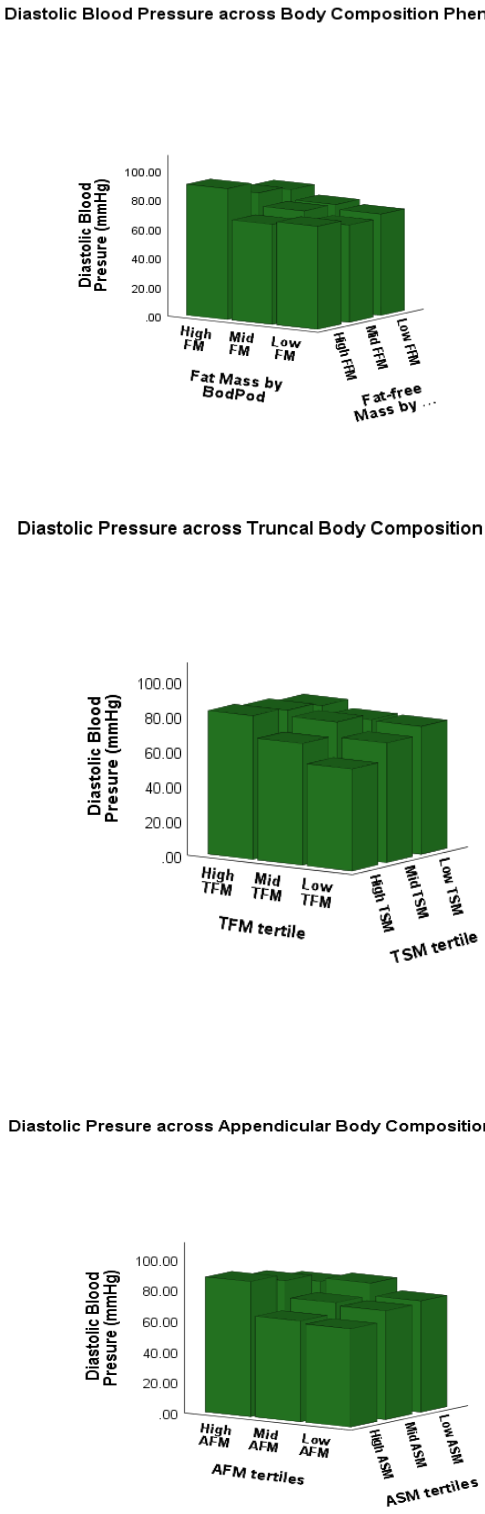


Figure 5.2 Diastolic blood pressure across body composition phenotypes; a) total, b) truncal, c) appendicular.

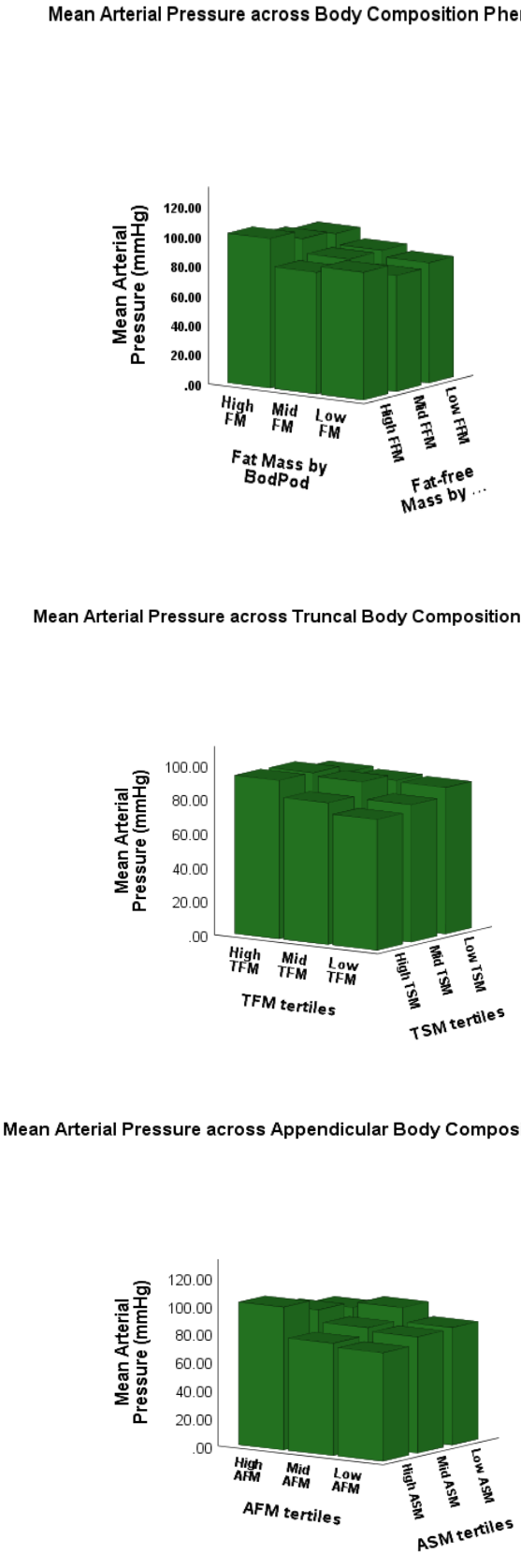


Figure 5.3 Mean arterial pressure across body composition phenotypes*; a) total, b) truncal, c) appendicular.*

5.4 Relative Body composition and systemic blood pressure

In order to explore the association between metabolic homeostasis and arterial function, fat mass to fat-free mass ratio and truncal fat mass to appendicular skeletal muscle mass ratio were created as the proxy measures of whole-body and segmental metabolic balance.

FM/FFM was significantly associated with DBP *(*β=17.61±6.4, $p<0.001$) but not SBP and pulse pressure. In contrast, TFM/ASM showed significant relationships with all three measures of blood pressure. Each 0.1point increase in TFM/ASM was respectively associated with 1.6mmHg *(*β=15.94±4.9, $p<0.01$) and 2.7mmHg *(*β=27.47±4.2, $p<0.001$) rise in SBP and DBP and 1.1mmHg *(*β=-11.38±4.01, $p<0.01$) decrease in pulse pressure (Figure 5.4). Hence, adults with segmental metabolic overload may have higher systolic and diastolic pressures as well as narrower pulse pressure even if their whole-body metabolic overload only affects the diastolic component of the arterial pressure.

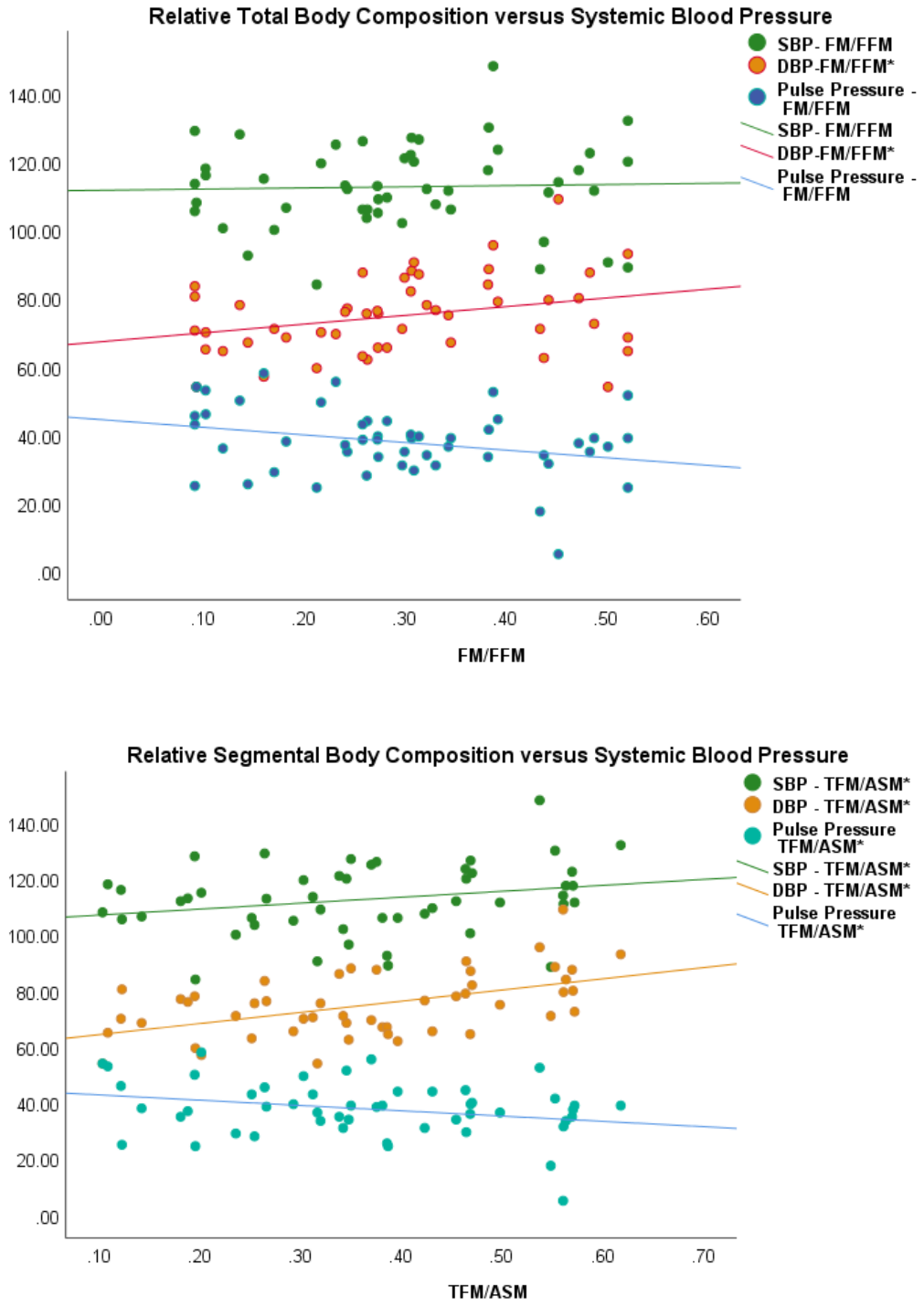


Figure 5.4. Systemic Blood Pressure relationship with a) total, b) segmental body composition phenotypes.

*significant relationship between measures of systemic pressure and relative body composition

TFM/ASM: truncal fat mass to appendicular skeletal muscle ratio; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Discussion

In this study, overfat SPs had higher SBP, DBP and MAP than SPs in the underfat and healthy-range categories of %BF. Both general and central obesity are well-known modifiable risk factor for hypertension. There is a large battery of literature on the independently positive association between adiposity and systolic as well as diastolic BP. Large-scale longitudinal studies also indicate that overweight or obese individuals are more likely to develop elevated SBP and DBP than normal or underweight individuals (Kannel *et al.*, 1987; Stevens *et al.*, 2001; Forman, Stampfer and Curhan, 2009; Koh *et al.*, 2011).

The observed sex-specific differences in the preceding correlations may stem from the higher intramuscular and ectopic fat infiltration in women (Miljkovic-Gacic *et al.*, 2008). It may also be speculated that the lower quantity of total and regional muscle mass affects BP-leanness association in females. Differential endocrine and metabolic actions of skeletal muscle tissue in the neurohormonal regulation of blood pressure cannot be ruled out too. It should not be forgotten that the study was underpowered for subgroup analysis and these observations may not accurately reflect the actual sex-specific relationships in the general population.

Another finding of this study was the significantly positive relationships of total and truncal fat mass with SBP, DBP and MAP and their negative relationship with PP. In contrast, the appendicular fatness was significantly related to DBP and MAP but not SBP.

There is compelling evidence on the associations of SBP and DBP with total, truncal and appendicular adiposity (Van Pelt *et al.*, 2002; Kim *et al.*, 2008; Hunter *et al.*, 2010; Park *et al.*, 2014; Ye *et al.*, 2018). As discussed thoroughly in the literature review, excessive (visceral) adiposity may induce hypertension via impaired renal pressure natriuresis due to the enhanced sodium reabsorption caused by renal compression and reduced tubular perfusion, metabolically intensified endothelial dysfunction, formation and progression of the atherosclerotic plaques and vascular stiffening, systemic and renal activation of sympathetic nervous system triggered by the altered sensitivity of mechano- and chemoreceptors (especially in the presence

of obstructive sleep apnoea), and BP-raising effects of the central leptin-melanocortin pathway and activation of renin-angiotensin-aldosterone system (Hall *et al.*, 2015). With regards to the leptin-melanocortin pathway, longstanding leptin resistance and hyperleptinaemia stimulates proopiomelanocortin (POMC) neurons in hypothalamus, brain stem, and spinal cord via leptin receptors and JAK-STAT, PI3K and MAPK signalling pathways, releasing α-melanocyte–stimulating hormone (α-MSH) which in turn activates melanocortin 4 receptors (MC4R) in sympathetic preganglionic neurons; this results in increased SNS activity and elevated arterial BP (do Carmo *et al.*, 2017).

Differential association of trunk and extremity adiposity with metabolic risk factors has been stressed in previous studies. In the Pennington Centre Longitudinal Study (PCLS), white and black American adults with high DXA-measured trunk and leg adiposity were respectively more and less likely to have 2 or more cardiometabolic risk factors, including elevated SBP or DBP (Hu *et al.*, 2011). As reported by Alexandersen *et al.*, truncal fat mass and peripheral lean mass were oppositely associated with aortic calcification in older Danish men. Severity of calcification was lower at highest tertile of DXA-measured appendicular lean mass in this population (Alexandersen *et al.*, 2006). Kim *et al.*, also showed that for any given %BF, higher DXA-determined arm and leg fat percentages were associated lower SBP in non-elderly women with abdominal adiposity. In contrast, higher trunk fat percentage predicted higher SBP in them (Kim *et al.*, 2008).

It was interesting to note that the distribution of fat mass changed the magnitude of the adiposity effect on the components of arterial BP. The lack of significant relationship between appendicular adiposity and SBP indicates that centrally distributed fat could be the main driver of the dynamic alterations in determinants of systolic pressure, including stroke volume, heart rate and arterial compliance. The significant association between total and segmental fatness and the mean arterial pressure can be mathematically explained by the greater contribution of diastolic pressure to the calculation of MAP; therefore, changes in the mean arterial pressure may be the reflection of the underlying changes in diastolic pressure. Comparable association of total as well as segmental fat mass with DBP and MAP demonstrates that central and peripheral adiposity may have similar adverse effects on the perfusion pressure and resistance of the peripheral arteries (Brzezinski, 1990).

Because PP was mathematically calculated as the difference between SBP and DBP, mostly non-significant relationships between pulse pressure and components of fat mass may be explained by the comparable effects of these components on SBP and DBP, with slightly greater influence on the diastolic component. and.

On this basis, it can be inferred that adiposity primarily contributes to the steady component of systemic blood pressure (as determined by cardiac output and vascular resistance) rather than the pulsatile component (influenced by the ejection fraction, compliance of the large arteries and wave reflections)(Darne *et al.*, 1989).

Contrary to the close relationship of adiposity with diastolic and mean arterial pressures, total leanness and segmental muscularity had significantly positive relationships with systolic pressure and pulse pressure. Higher SBP in the individuals with larger lean, particularly skeletal muscle, compartment may be due to the increased cardiac output to sustain adequate perfusion of this expanded site of metabolic activities. Over time, this augmented mechanical stress would induce remodelling of the vasculature, leading to the thickening and reduced elasticity of the large arteries (Leischik *et al.*, 2014). This cycle of increased cardiac output and arterial stiffness could manifest as elevated systolic BP (Martyn and Greenwald, 1997). Owing to the concomitant decrease in peripheral resistant of the muscular arteries (caused by the endothelium-dependent and endothelium-independent relaxation of resistant arteries), diastolic pressure may drop or remain unchanged (Rowell, 1993). The counterbalancing effects of changes in SBP and DBP may result in the maintenance of the mean arterial pressure and subsequently perfusion pressure. This can explain no significant relationship of muscle mass with diastolic or mean arterial pressures. The same logic can be offered for the association between pulse pressure and skeletal muscle mass.

The widening of pulse pressure in more muscular SPs could reflect the opposite changes in systolic and diastolic components of the arterial pressure (Homan and Cichowski, 2018). In addition, pulse pressure has been suggested as a measure of pulsatile hemodynamic stress and a marker of arterial stiffness (Dart *et al.*, 2001). Thus, it could be postulated that leanness, more specifically skeletal muscle mass, is more related to the pulsatile component of systemic pressure and higher degrees of muscularity may indicate the increased arterial stiffening, disruption in the

propagation of the forward pressure wave and reflection of the backward pressure wave, attenuation of central to peripheral pressure amplification, and dissipation of the stiffness gradient. In this setting, the wave reflection occurs earlier during systole rather than diastole and reflected waves run into the forward waves, amplifying systolic pressure and diminishing diastolic pressure (London and Pannier, 2010). It is worth mentioning that peripherally measured pulse pressure may not be an accurate indicator of pulse pressure and elastic properties of the aorta and conduit arteries (Izzo Jr, 2014).

The evidence surrounding the effect of lean mass on BP is conflicting. Cross-sectional studies suggest the protective role of skeletal muscle mass against adverse cardiometabolic outcomes, including hypertension and arterial stiffness (Atlantis *et al.*, 2009; Ochi *et al.*, 2010; Prasad *et al.*, 2016). On the contrary, recent studied on the predominantly young and healthy subjects have revealed positive associations of total and regional lean mass indices with SBP and the risk of hypertension across different ethnicities (Wang *et al.*, 2009; Prasad *et al.*, 2016; Zhao *et al.*, 2017; Ye, 2018). Importantly, these associations are modified by adiposity. Peppa *et al.*, in a study of non-smoking postmenopausal women found a significant synergistic effect of lean mass index and WC on the metabolic risk factors, including SBP and DBP (Peppa *et al.*, 2014). Similarly, in a study of urban Chinese adults, when the effect of total skeletal muscle on the risk of hypertension and the association of appendicular lean mass indices with SBP and DBP became significantly positive after controlling for %BF and AOI (Ye *et al.*, 2018). As a more concrete evidence of muscle-fat interaction, Zhao *et al*., showed that progressive attenuation in calf muscle increased the risk of incident hypertension in black men after adjustment for insulin resistance, WC and IMAT (Zhao *et al.*, 2017). This underscores the crucial role of global and regional metabolic crosstalk between lean and fat compartments in the regulation of BP. It should also be noted that the studies which pointed to a beneficial impact of leanness on the measures of vascular function did not include a heterogenous population, used anthropometric proxies for leanness, or did not partial out the confounding effect of adiposity. In addition to the putative role of intramuscular fat infiltration in inducing insulin dysregulation (Eastwood *et al.*, 2014) and RAAS-mediated vascular dysfunction (Gastaldelli and Basta, 2010), muscle-specific mechanisms suggested to be involved in the BP-rising effects of muscularity include

LVH and carotid wall thickening, arterial stiffness (Leischik *et al.*, 2014; Moreno *et al.*, 2015), myofiber type shift in hypertrophied muscles (DiCesare *et al.*, 2017) and SNS activation (Saito, Iwase and Hachiya, 2009).

In addition, appendicular fat and lean mass have been shown to be significantly associated with the calibre, compliance and stiffness of the peripheral arteries (Ferreira *et al.*, 2004). In hypertensive and normotensive individuals, pulse pressure as a surrogate measure of arterial stiffness and LV afterload, exhibits inverse association with endothelial function in conduit and resistance vessels (Ceravolo *et al.*, 2003; Nigam *et al.*, 2003; Wiesmann *et al.*, 2004; Mceniery *et al.*, 2006) and thereby is directly related to the risk of atherosclerosis and CHD (Schächinger, Britten and Zeiher, 2000; Perticone *et al.*, 2001). Thus, the positive relationship between muscle mass and PP the study population may be translated into a higher long-term cardiometabolic risk.

A major finding of this research was the significant difference of DBP and MAP across total, truncal, and appendicular body composition phenotypes. Whereas SPs with high total and truncal fatness and leanness had higher diastolic pressure than SPs with other total and truncal body composition phenotypes. Also, SPs with lower fat but higher muscle content in their limbs had lower diastolic pressure as compared to other SPs.

When examined in the context of metabolic load - metabolic capacity model, FM/FFM ratio as a measure of whole-body metabolic balance was only significantly associated with diastolic pressure whilst TFM/ASM as a measure of segmental metabolic balance demonstrated significant associations with SBP, DBP and pulse pressure. This finding suggests that adults with metabolic overload at whole-body level may have more resistant muscular arteries whereas those with segmental metabolic overload (with greater quantity of truncal fat as compared to appendicular muscle) may have developed haemodynamic alterations in both steady and pulsatile determinants of arterial pressure.

Relative contribution of skeletal muscle and adipose tissues, as determinants of metabolic balance, to haemodynamic changes has been identified in adults. In the Korean Sarcopenic Obesity Study (KSOS), skeletal muscle to visceral fat ratio was inversely related to cardiometabolic risk factors and brachial pulse wave velocity

(baPVW), denoting a link between the favourable segmental balance between metabolic load-metabolic capacity and arterial stiffness (T. N. Kim *et al.*, 2011). The independent but opposite effects of visceral fat mass and appendicular muscle mass on baPVW has also been demonstrated in postmenopausal women with diabetes (Tanaka, Kanazawa and Sugimoto, 2016). Such effect may be mediated by the dominance of pro-inflammatory adipokines and myokines, reduced insulin sensitivity and impaired lipid and glucose metabolism, oxidative stress that lead to structural and dynamic changes in vascular system (Giudice and Taylor, 2017; Li *et al.*, 2017; Chen *et al.*, 2019). Therefore, metabolic homeostasis can be linked to haemodynamic properties of the cardiovascular system via reciprocal effects of adipose and lean tissues.

Although this research is the first study that quantitatively explores the association between total and segmental body composition phenotypes and systemic blood pressure in healthy adults from the perspective of metabolic homeostasis and haemodynamic stability, it has several limitations. Firstly, it has a cross-sectional design and small sample size; this limits the generalisability of the findings, evaluation of the causal relationship, statistical power and the accuracy of subgroup analysis. Moreover, the use of BIA in the assessment of body composition may introduce some level of estimation error, granted that the segmental multifrequency method improves the accuracy of estimation. Additionally, the analysis of associations did not include an exhaustive set of potential confounders.

Further research is warranted to determine the nature of these associations and the potential role of body composition phenotyping in the assessment and management of haemodynamic abnormalities by employing more direct measures of endothelial function, arterial stiffness, intima-media thickness and vascular resistance as well as more accurate methods of body composition assessment such as DXA or imaging techniques.

Chapter 6

Body Composition and Lung Function

The relationships between spirometric indices and anthropometric as well as body composition measures were examined using Pearson's correlation test. Overlay scatterplots were drawn to display reciprocal correlations of spirometric parameters with appendicular lean versus fat compartments of body composition. To identify significant covariates of spirometric indices, multiple liner regression with back-ward elimination was undertaken using heteroscedasticity-consistent standard error estimators (Hayes and Cai, 2007). The main and interaction effects of stature-normalised fat and lean body compartments on pulmonary function were analysed in the PROCESS using OLS regression models adjusted for age, sex, ethnicity, height, neck circumference, calf circumference, grip strength as well as systolic and diastolic pressures. The smoking status was not considered in the prediction models as a large number of participants were not current smokers (48 out of 50 SPs). The quality of predictive models was measured by the mean standard error (MSE). For all models, lean component was set as the moderator and the values of the moderator wherein the main effect of fat component on the spirometric outcome shifted from non-significant to significant were defined. The conditional influence of total and segmental fat mass on measures of lung function was probed at three levels, *i.e.*, 16^{th}, 50^{th}, and 84^{th} percentiles of the corresponding lean mass. The effects of total and segmental fat on lung function parameters were plotted at low, medium, and high levels of the corresponding lean components using visualisation data output from the PROCESS.

Results

6.1 Anthropometric measures and lung function

Among lung function parameters, $FEF_{25-75\%}$ did not show any significant relationship with anthropometric measures. In total population, NC, AC, WC and ABSI were the only significant anthropometric correlates of spirometric indices. In

this regard, ABSI was the strongest correlate of FEV_1 (r=-.52, p<0.001), and FVC (*(*r=-.49, p<0.01), whilst FEV_1/FVC (r=.36, p<0.05) was most closely related to WC (r=-.45, p<0.001)

Both ABSI and WC demonstrated significant relationships with all spirometric indices albeit in the opposite directions. Larger waist and neck circumferences and greater conicity index correlated significantly with higher FEV_1 (r=.38, p<0.01; r=.38, p<0.01; r=.34, p<0.05) and FVC (r=.36, p<0.01; r=.40, p<0.01; r=.36, p<0.05). AC was only significantly related to FEV_1 (r=.30, p<0.05). BMI, CC, WHR and WHtR did not display significant correlations. (Figure 6.1).

Notably, the relationships between ABSI and spirometric parameters were in the opposite direction to those of other anthropometric measures. SPs with higher ABSI had lower FEV_1 and FVC but higher FEV_1/FVC ratios. Conversely, SPs with higher NC, WC and CI had higher FEV_1 and FVC but lower FEV_1/FVC ratios.

This may indicate a positive association between upper body fatness (even after adjustment by height and body weight) and vital capacity and expiratory airflow in otherwise healthy adults, with greater influence of fatness on FVC than FEV_1. When the influence of body size and BMI on WC is controlled in the ABSI, the association of the adjusted WC (as a measure of visceral adiposity) and dynamic lung function is reversed. As shown in previous chapters, increased ABSI could be a good indicator of depleted lean and muscle mass.

In addition, the increased neck circumference and unadjusted waist circumference could reflect expanded fat and lean mass, with NC being a better indicator of leanness and WC being a stronger measure of fatness. Hence, higher FVC and FEV_1 in SPs with larger perimeters of neck and abdomen may also be linked to increases in their fat-free mass and skeletal muscle mass.

To clarify this, the relationship of BIA-derived quantities of both total and regional fat and lean compartments with spirometric indices were examined.

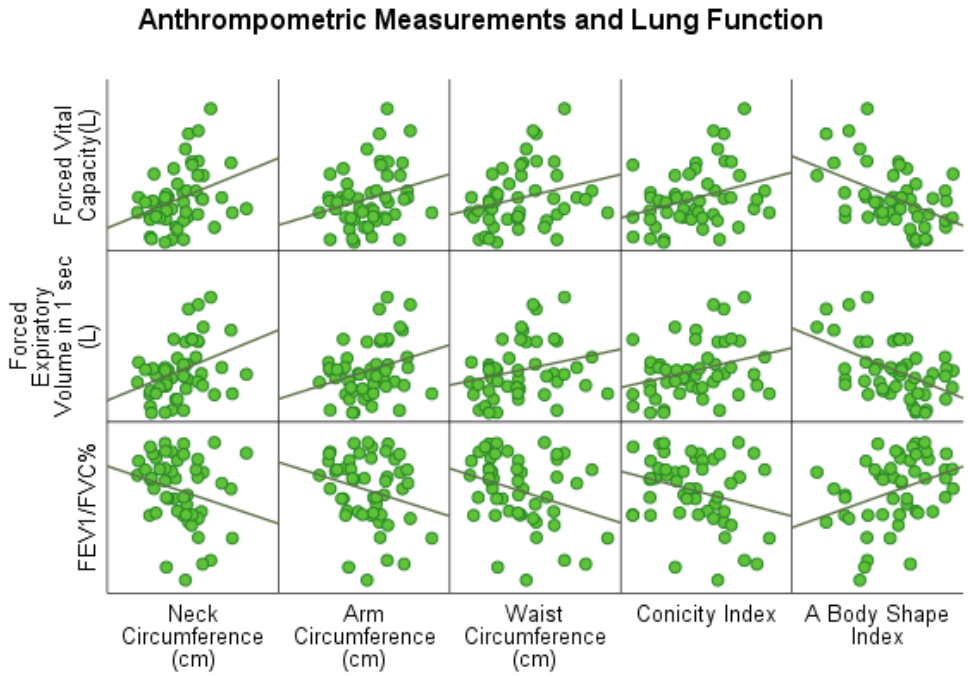


Figure 6.1. Significant anthropometric correlates of the spirometric parameters. *FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.*

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6.2 Absolute body composition and lung function

BIA-derived estimates of total and segmental lean mass exhibited significant correlations with all spirometric parameters in total SPs (Table 6.1) although FEV_1 and FVC showed closer relationships than FEV_1/FVC and $FEF_{25-75\%}$. Unlike other indices, FEV_1/FVC correlated negatively with all measures of lean mass, denoting that changes in leanness associates with larger changes in FVC than FEV_1.

Concerning measures of fatness, however, significant relationships were observed only between FEV_1 (r=-.51 and -.57, p<0.01) and FVC (r=-.48 and -.53, p<0.01) with AFM and LFM.

This observation lends further support to the previously addressed possibility that direct relationship of FVC and FEV_1 as well as the inverse relationship of FEV_1/FVC with neck circumference and unadjusted waist circumference in healthy adults may actually represent the correlation between dynamic lung function and the status of lean compartments rather than the adiposity status. Relevantly, the previously observed opposite association of ABSI with spirometric parameters as compared to other anthropometric measures was replicated for BIA-estimated fat mass and skeletal muscle mass.

While measures of muscularity all correlated positively with FVC and FEV_1, measures of adiposity showed negative correlations with these spirometric indices. Among measures of fatness, only appendicular fat mass was found to be significantly related to FVC and FEV_1.

Table 6.1. Lung function and body composition

	Spirometric parameter	Lean compartment					Fat compartment				
		FFM	TSM	ASM	USM	LSM	FM	TFM	AFM	UFM	LFM
Male	FEV_1 (L)	0.39	0.34	0.44*	0.34	0.48*	-0.39	-0.35	-0.44*	-0.34	-0.49*
	FVC (L)	0.29	0.24	0.34	0.18	0.38	-0.27	-0.23	-0.34	-0.25	-0.36
	FEV_1 /FVC	0.03	0.09	-0.09	0.06	-0.15	-0.16	-0.15	-0.12	-0.11	-0.06
	$FEF_{25-75\%}$ (L/s)	0.32	0.35	0.24	0.24	0.23	-0.30	-0.26	-0.32	-0.23	-0.30
Female	FEV_1 (L)	-0.36	-0.35	-0.33	-0.17	-0.23	-0.16	-0.11	-0.17	-0.21	-0.14
	FVC (L)	-0.41	-0.35	-0.37	-0.20	-0.29	-0.24	-0.21	-0.22	-0.33	-0.16
	FEV_1 /FVC	0.17	-0.01	0.13	0.08	0.15	-0.03	0.04	-0.06	0.08	-0.07
	$FEF_{25-75\%}$ (L/s)	-0.20	-0.22	-0.27	-0.04	-0.20	0.07	0.08	0.10	0.07	0.14
Total	FEV_1 (L)	.60***	.57***	.63***	.61***	.64***	-.23	.01	-.51**	-.22	-.57**
	FVC (L)	.56***	.53***	.58***	.55***	.60***	-.18	.04	-.48**	-.21	-.53**
	FEV_1 /FVC	-.33*	-.32*	-.39*	-.34*	-.40*	-.09	-.20	.15	.00	.21
	$FEF_{25-75\%}$ (L/s)	.34*	.34*	.29*	.34*	.30*	-.14	-.02	-.25	-.09	-.25

Values are presented as r.

For all correlations in male, female, and total participants, n=22, 28, and 50, respectively.

**p<0.05; **p<0.01; ***p<0.001*

All compartments were measured by Tanita SEG-MF Bioelectrical Impedance Analyser.

FFM: fat-free mass; TSM: trunk skeletal muscle mass; ASM: appendicular skeletal muscle mass; USM: upper limb skeletal muscle mass; LSM: lower limb skeletal muscle mass TFM: trunk fat mass; AFM: appendicular fat mass; UFM: upper limb fat mass; LFM: lower limb fat mass; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

Stratified by sex, significant correlations were found only between FEV_1 and appendicular, more specifically, the lower limb skeletal (r=.44 and .48, p<0.05) and fat mass (r=-.44 and -.49, p<0.05) in male SPs (Figure 6.2). There was no significant relationship between spirometric indices and body composition compartments in female SPs. For any given lung function parameter, all components of lean and fat compartments demonstrated oppositely directed relationships.

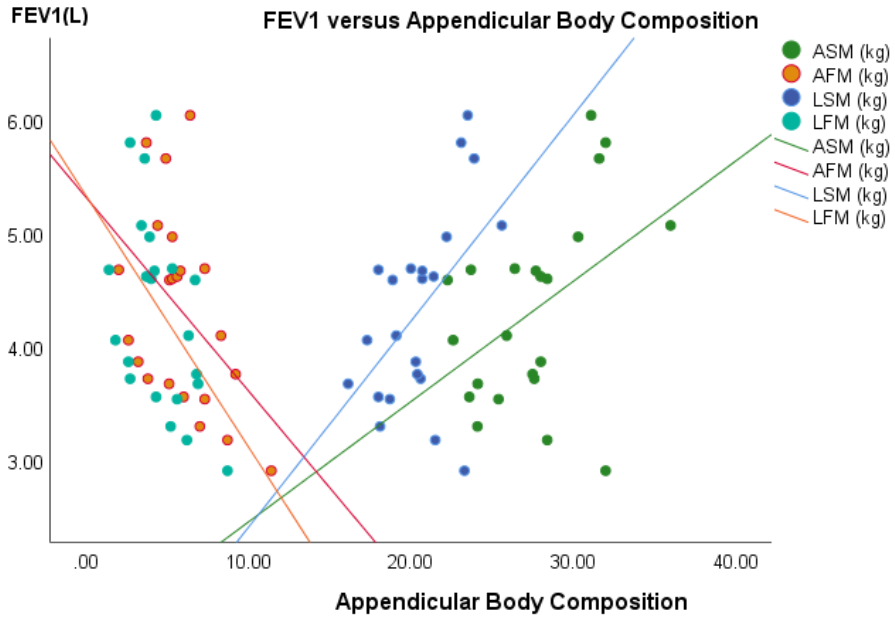


Figure 6.2. Equally significant but oppositely directed relationship between FEV_1 and appendicular as well as lower limb lean versus fat mass in male SPs.

ASM: appendicular skeletal muscle mass; LSM: lower limb skeletal muscle mass AFM: appendicular fat mass; LFM: lower limb fat mass; FEV_1: forced expiratory volume in 1s

6.3 Stature-normalised body composition and lung function

To explore the association of total and segmental fatness and leanness with dynamic lung function more thoroughly, the effect of potential confounders was analysed in multiple linear regression models by using backward elimination method. As a large proportion of SPs were not current smokers, smoking status was not used in the models. Subsequently, the explanatory variables with significant contributions, *i.e.*, age, sex, height, ethnicity, neck circumference, calf circumference, grip strength, and systemic blood pressure were included in the predictive models.

Regression models for all pairs of stature-normalised fat and lean components significantly explained variations in FEV_1(R^2=.77 to .79, p<0.001), FVC (R^2=.72 to .74, p<0.001) and $FEF_{25-75\%}$ (R^2=.32 to .34, p<0.001). For all spirometric parameters, stature-adjusted total and segmental fat mass indices demonstrated opposite effects on FEV_1 and $FEF_{25-75\%}$ at low versus high levels of their corresponding lean mass indices.

As shown in Table 6.2, total fat and lean mass indices contributed significantly to the prediction of FEV_1 (β=.46 and 0.10, p<0.001) and $FEF_{25-75\%}$ (β=.90 and 0.37, p<0.001) but not FVC. White ethnicity (β=-.051, p<0.001), sex (β=-.901, p<0.001), height (β=.047, p<0.001), calf circumference (β=.051, p<0.01), grip strength (β=-.017, p<0.01) and DBP (β=-.016, p<0.001) were significant covariates of FEV_1 whereas age (β=.038, p<0.001), sex (β=-.529, p<0.05), height (β=.042, p<0.001), grip strength (β=-.044, p<0.001) and SBP (β=-.018, p<0.01) were significant contributors to the variations in $FEF_{25-75\%}$.

Table 6.2. Main and interaction effects of stature-normalised total fat and lean mass indices on spirometric parameters

Spirometric parameter	FMI	FFMI	*p*-interaction	R^2 (MSE)	Significance region(s)
FEV_1 (L)	0.46^{***} (0.23,0.68)	0.10^{**} (0.03,0.16)	0.000	0.78^{***}(0.19)	17.55
FVC (L)	0.21 (–0.13, 0.53)	-0.03 (-0.13,0.07)	0.083	0.73^{***}(0.39)	19.8
$FEF_{25-75\%}$ (L/s)	0.90^{***} (0.43,1.35)	$.37^{***}$ (0.22, 0.52)	0.000	0.34^{***}(0.86)	14.73, 18.6

Values are presented as β(95% CI).

**p<0.05; **p<0.01; ***p<0.001*

All compartments were measured by Tanita SEG-MF Bioelectrical Impedance Analyser.

OLS regression models were adjusted for age, sex, height, ethnicity (white vs. non-white), neck circumference, calf circumference, grip strength, and systemic blood pressure.

Regions of significance are defined as the values of the lean mass index where the association between total or segmental fat mass and spirometric indices transitioned from non-significant to significant.

MSE: mean squared error; FFMI: fat-free mass index; FMI: fat mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

To investigate the combined effect of regional fat and lean components on pulmonary function, the interaction effect of total fat mass and fat-free mass as well as truncal and appendicular fat mass and skeletal muscle mass were explored using the moderation analysis via PROCESS.

As portrayed in Figure 6.3, the moderation analysis revealed that FMI associated significantly with FEV_1 only at FFMI values above 17.5 kg/m^2. Thus, FMI was a significantly negative predictor of FEV_1 in SPs with high (84^{th} percentile) FFMI (β=-.12; 95%CI (-.18, -.07), p<0.001).

Notwithstanding the absence of significant main effects, height-adjusted total fat and fat-free mass demonstrated significant interaction on FVC. Each 1kg/m^2 increase in FMI was significantly predictive of 108ml decrease in FVC at 84^{th} percentile of FFMI (β=-.108; 95%CI (-0.043, -0.214), p<0.05).

With regards to $FEF_{25-75\%}$, significant interactions occurred at FFMI values below 14.7 kg/m^2 and above 18.6 kg/m^2. Nevertheless, the effect of FMI on $FEF_{25-75\%}$ was mainly conditioned at 84^{th} percentile; therefore, increased total fat mass index predicted reduced $FEF_{25-75\%}$ in SPs with high FFMI *(*β=-.17; 95%CI (-.26, -.06), p<0.01).

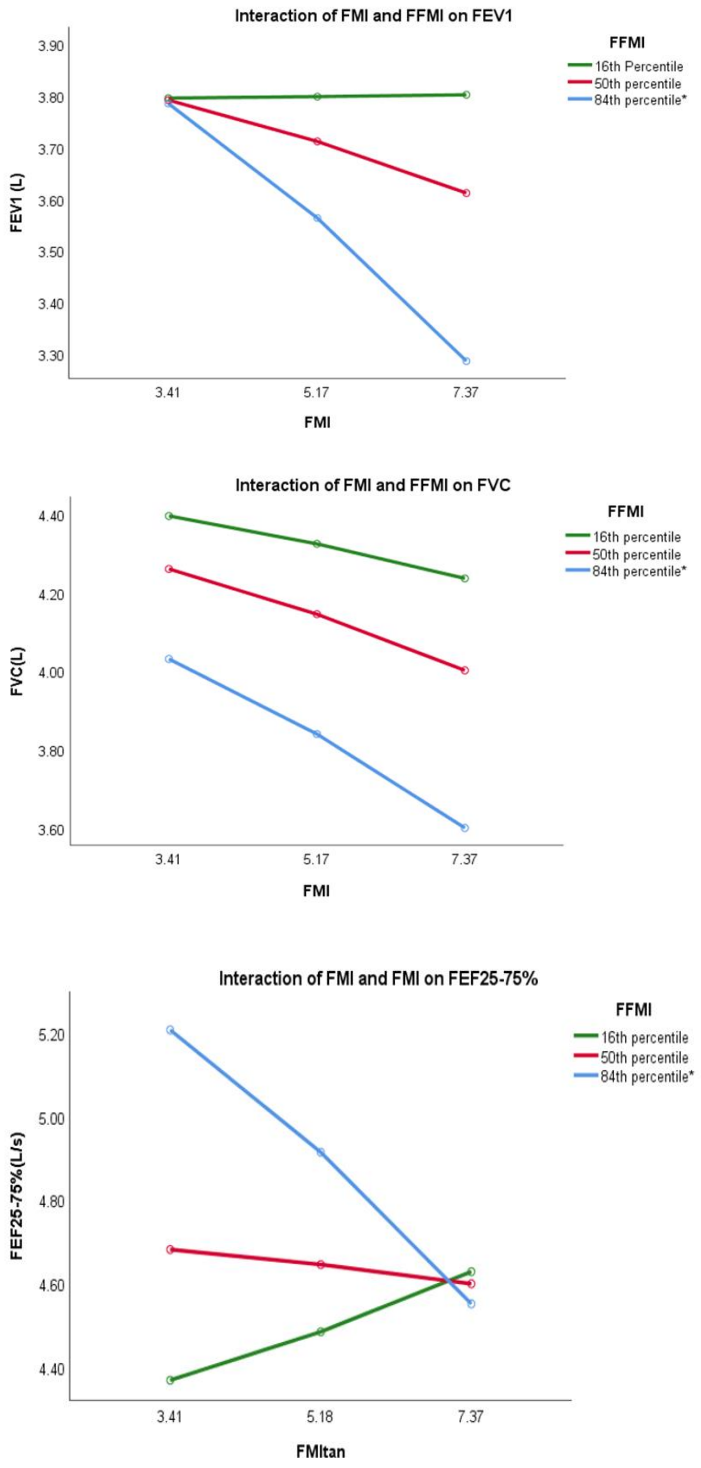


Figure 6.3. Interactions of stature-normalised total lean and fat mass indices on (a) FEV_1, (b) FVC, (c) $FEF_{25-75\%}$.

**lean index level with significant effect of fat index on spirometric parameters.*

16^{th}, 50^{th} and 84^{th} percentiles of FFMI respectively represent FFMI values of 15.77 kg/m^2, 17.39 kg/m^2, and 20.17 kg/m^2.

FFMI: fat-free mass index; FMI: fat mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

As reflected in Table 6.3, stature-adjusted truncal fat *(*β=0.92, *p*<0.001) and skeletal muscle indices (β=0.10, p<0.05) demonstrated significant associations with FEV_1. For FVC, only truncal fat mass index was a significant predictor (β=0.94, *p*<0.001). Conversely, only truncal skeletal mass index could significantly predict $FEF_{25-75\%}$ *(*β=0.47, *p*<0.01) (Table 6.3). Significant covariates of FEV_1 were sex (β=-0.998, *p*<0.001), ethnicity (β=-0.062, *p*<0.001), NC (β=-0.030, *p*<0.05), and DBP (β=-0.019, *p*<0.001) while FVC associated significantly with sex (β=-1.461, *p*<0.001), ethnicity (β=0.286, *p*<0.001), height (β=0.050, *p*<0.001), NC (β=-0.046, *p*<0.01), CC (β=0.057, *p*<0.05), and DBP (β=-0.029, *p*<0.001).

Table 6.3. Main and interaction effects of stature-normalised truncal fat and lean mass indices on spirometric parameters

Spirometric parameter	TFMI	TSMI	*p*-interaction	R^2 *(MSE)*	Significance region(s)
FEV_1 (L)	0.92^{***} (0.48,1.35)	0.14^{*} (0.02,0.25)	0.000	0.78^{***} (0.19)	8.07,9.97
FVC (L)	0.94^{**} (0.35,1.52)	-0.02 (-0.20,0.16)	0.001	0.74^{***} (0.37)	8.60,11.31
$FEF_{25-75\%}$ (L/s)	0.74 (-0.33,1.80)	0.47^{**} (0.16,0.77)	0.093	0.32^{***} (0.88)	9.67

Values are presented as β(95% CI)

**p<0.05; **p<0.01; ***p<0.001*

All compartments were measured by Tanita SEG-MF Bioelectrical Impedance Analyser.

OLS regression models were adjusted for age, sex, height, ethnicity, neck circumference, calf circumference, grip strength, and systemic blood pressure.

Regions of significance are defined as the values of the lean mass index where the association between total or segmental fat mass and spirometric indices transitioned from non-significant to significant.

MSE: mean squared error; TSMI: truncal skeletal mass index; TFMI: truncal fat mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

Furthermore, TFMI and TSMI interacted significantly on spirometric indices such that high TFMI values predicted decreased FEV_1 *(*β=-.184; 95%CI (-.268, -.101), $p<0.001$) in SPs with high TSMI (>9.97 kg/m^2). At TSMI values below 8.60 kg/m^2, higher TFMI predicted higher FVC *(*β=.132; 95%CI (-.002, .26), $p>.05$) while it was a predictor of lower FVC *(*β=-.093; 95%CI (-.203, .017), $p>.05$) at TSMI values above 11.31 kg/m^2 (Figure 6.4). TSMI also moderated the influence of TFMI on $FEF_{25-75\%.}$ At high level of TSMI, $FEF_{25-75\%.,}$ declined by about 280ml/s per 1 kg/m^2 increase in TFMI *(*β=-.278; 95%CI (-.466, -.089), $p<0.01$).

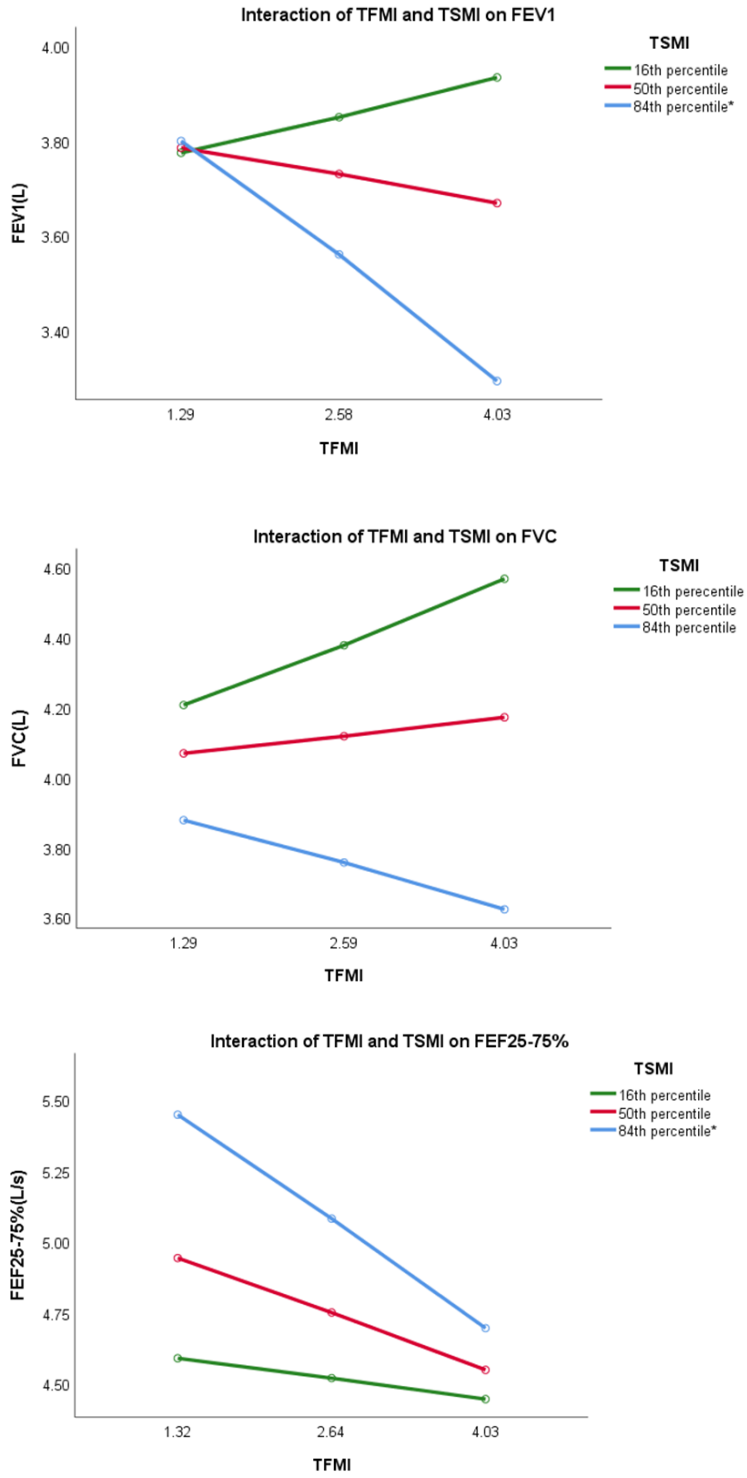


Figure 6.4 Interaction effects of height-normalised truncal lean and fat mass indices on (a) FEV_1, (b) FVC, (c) $FEF_{25-75\%}$.

**lean index level with significant effect of fat index on spirometric parameters.*

16^{th}, 50^{th} and 84^{th} percentiles of TSMI respectively represent TSMI values of 8.64 kg/m^2, 9.65 kg/m^2, and 11.10 kg/m^2.

TSMI: truncal skeletal muscle index; TFMI: trunk fat mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

As presented in Table 6.4, appendicular fat and muscle mass indices had significant main and interaction effects on FEV_1 *(*β=1.21 and .31, $p<0.001$), FVC *(*β=.94, $p<0.01$; and .17, $p>0.05$), and $FEF_{25-75\%}$ *(*β=1.88 and .68, $p<0.001$). Sex (β=-.857 and -.1.225, $p<0.001$), ethnicity (β=.276, $p<0.001$ and β=.230, $p<0.01$), height (β=0.046 and .056, $p<0.001$), NC (β=-.026, $p<0.05$ and β=-.057, $p<0.001$), CC (β=.041, $p<0.05$ and β=.078, $p<0.05$) and DBP (β=-.019 and -.023, $p<0.001$) also made significant contributions to the prediction of variations in FEV_1 and FVC, respectively. Age (β=.034, $p<0.001$), height (β=.049, $p<0.001$) and grip strength (β=-.041, $p<0.01$) were the significant covariates of $FEF_{25-75\%}$.

Table 6.4. Main and interaction effects of stature-normalised appendicular fat and lean mass indices on spirometric parameters

Spirometric parameter	AFMI	ASMI	*p*-interaction	R^2 (*MSE*)	Significance region(s)
FEV_1 (L)	1.21^{***} (0.78,1.65)	0.31^{***} (0.18,0.45)	0.000	0.79^{***} (0.18)	6.18,7.49
FVC (L)	0.94^{**} (0.32,1.55)	0.17 (-0.09,0.42)	0.003	0.73^{***} (0.38)	8.21
$FEF_{25-75\%}$ (L/s)	1.88^{***}(0.88,2.89)	0.68^{***}(0.31,1.06)	0.000	0.33^{***} (0.87)	6.89,8.81

Values are presented as β(95% CI)

**p<0.05; **p<0.01; ***p<0.001*

All compartments were measured by Tanita SEG-MF Bioelectrical Impedance Analyser.

OLS regression models were adjusted for age, sex, height, ethnicity, neck circumference, calf circumference, grip strength, and systemic blood pressure.

Regions of significance are defined as the values of the lean mass index where the association between total or segmental fat mass and spirometric indices transitioned from non-significant to significant.

MSE: mean squared error; ASMI: appendicular skeletal mass index; AFMI: appendicular fat mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

The effect of AFMI on lung function depended upon the values of ASMI (Figure 6.5). In SPs with high ASMI (84th percentile), FEV_1 decreased by approximately 390ml per 1kg/m^2 increase in AFMI *(*β=-0.386; 95%CI (-.524, -.249), p<0.001) while in those with low ASMI (16th percentile), it increased by 86ml per unit increase in AFMI *(*β=.086; 95%CI (-.206,.033), p>0.05). A similar pattern was observed for the conditional effect of AFMI on FVC, with high AFMI being associated with impaired FVC at 84th percentile of ASMI *(*β=-.39; 95%CI (-.70, -.07), p<0.05). Two regions of significance were found for the interaction effect of AFMI and ASMI on $FEF_{25-75\%}$. At ASMI values above 8.81 kg/m^2, AFMI acted as a negative predictor *(*β=-.342; 95%CI (-.644, -.041), p<0.05) whereas at ASMI values below 6.89 kg/m^2, it showed a positive association with $FEF_{25-75\%}$ *(*β=.315; 95%CIs (.089, .541), p<0.001).

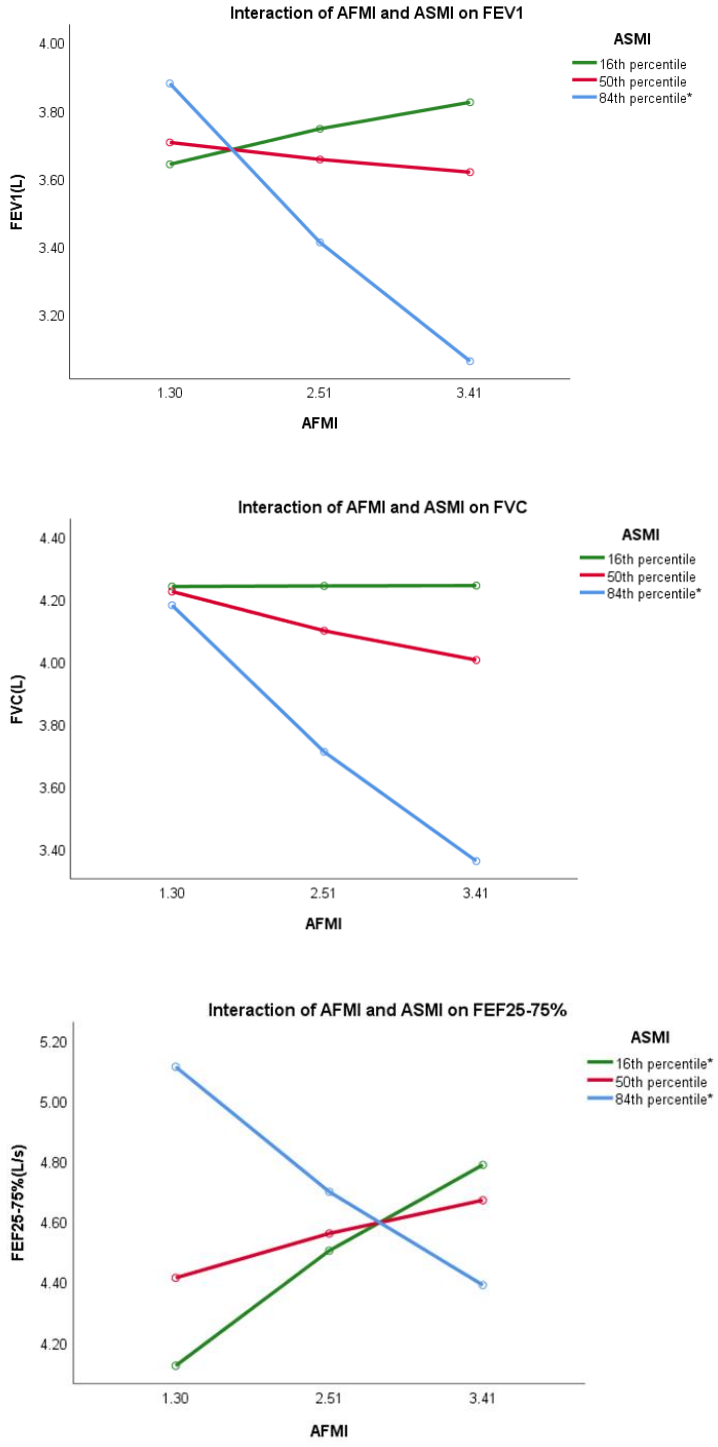


Figure 6.5 Interaction effects of height-normalised appendicular lean and fat mass indices on (a) FEV_1, (b) FVC, (c) $FEF_{25-75\%}$.

**lean index level with significant effect of fat index on spirometric parameters.*

16^{th}, 50^{th} and 84^{th} percentiles of ASMI respectively represent ASMI values of 6.41 kg/m^2, 7.20 kg/m^2, and 9.09 kg/m^2.

ASMI: appendicular skeletal muscle index; AFMI: appendicular fat mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

In a more interpretive sense, FEV_1 and $FEF_{25-75\%}$ declined with increasing FMI and AFMI at high levels of FFMI and ASMI. The opposite associations were observed at low values of FFMI and ASMI. In comparison, FEV_1 and FVC were negatively associated with TFMI at high TSMI values while the association was positive at low TSMI values. It is also worth mentioning that the gap in the absolute values of FEV_1 and FVC among SPs with lowest versus highest ASMI and TSMI levels widened progressively with increasing AFMI and TFMI. Thereby, SPs with the highest appendicular or truncal fat to muscle ratio had the highest FEV_1 and (to a lesser extent) FVC while those with the lowest segmental body composition ratios had the lowest FEV_1 and FVC. Additionally, at high levels of total fat-free mass the slope of FEV_1 and FVC associations with fat components became steeper when the corresponding fat mass level exceeded the middle range. In contrast, the rate of AFMI-related FEV_1 and FVC reductions at high ASMI level declined when the appendicular fat mass approached the higher range. Conversely, the $FEF_{25-75\%}$ gap among SPs with low versus high FFMI or ASMI became considerably narrower with increasing total and appendicular fat mass. As a result, participants with low FMI or AFMI exhibited the fastest mid-expiratory rates (highest $FEF_{25-75\%}$) at the highest FFMI or ASMI levels.

Therefore, it could be conjectured that the deleterious impact of incremental total, truncal and appendicular fat accumulation on FVC, FEV_1 and mid-expiratory flow rate in healthy adults would appear or heighten only if the respective lean or muscle compartments are already expanded.

Discussion

The first noticeable finding of this study about the link between body composition and pulmonary function was the oppositely directed association of ABSI versus all other anthropometric measures with spirometric indices. Whereas all other anthropometric measures showed inverse relationships with FEV_1 /FVC and direct relationships with FEV_1 and FVC in the entire population, ABSI was inversely related to FEV_1 and FVC and directly related to FEV_1 /FVC. This trend was replicated when BIA-estimated measures of fat and lean compartments were used. Whilst total and appendicular fatness demonstrated direct relationship with FEV_1 /FVC and inverse relationships with FEV_1 and FVC similar to the pattern observed for ABSI, total leanness as well as truncal and appendicular muscularity showed a reverse pattern comparable to all other anthropometric measures. An interesting finding was the direct significant relationship of total, truncal and appendicular lean/muscle mass with $FEF_{25-75\%}$ in the entire population.

The above findings indicate that anthropometric measures mostly represent the effect of lean rather than fat compartments on the dynamic lung function in otherwise healthy adults. In addition, ABSI may be only anthropometric index that could be used as a surrogate of the adiposity status in the assessment of respiratory performance among adults who are not in the extremes of body mass.

These observations also demonstrate that adults without clinically apparent pulmonary disease who have lower degrees of overall leanness or smaller amounts of skeletal muscle in their trunk or limbs could have restricted lung expansion, airway distensibility or elastic recoil as well as narrowed small airways due to reduced respiratory muscle strength, increased airway resistance, altered anatomical and physiological properties of the respiratory system and a pro-inflammatory status in the lung tissue. This would manifest as lower FEV_1, FVC and $FEF_{25-75\%}$ as well as an increased FEV_1 /FVC, denoting some degrees of upper airway restriction with the possibility of coexisting small airway obstruction. The independently positive association between total and segmental leanness or muscularity and lung function in apparently healthy young to middle-aged adults has been reported by previous studies (Martín Holguera *et al.*, 2017; Park *et al.*, 2018). As fully explained in chapter 2, the expansion of lean, particularly muscle compartment has a favourable

impact on lung volume and ventilatory capacity, due in part to the augmented strength of respiratory muscles , improved mechanics of respiration and more efficient ventilation in individuals with or without lung disease (Muggensturm *et al.*, 2013; Aliverti, 2016).

On the contrary, as extensively discussed in chapter 2, excessive fatness exerts detrimental effects on several aspects of respiratory physiology (lung volume, lung compliance, airway resistance, ventilation and gas exchange) even in otherwise healthy adults (Salome, King and Berend, 2010), leading to significant declines in FEV_1 and FVC together with no change or slight increases in FEV_1 /FVC (Sutherland *et al.*, 2016). It is unclear why appendicular fat mass was the only fat compartment which showed significant relationship with spirometric parameters; however, a similar observation has been reported by Scott *et al.* who found a significantly negative correlation between arm but not leg fat mass and FVC in overweight/obese female Australians with stable asthma (Scott *et al.*, 2012). In that study, arm but not leg fatness was associated with serum leptin and bronchoalveolar eosinophil percentage in male patients

In accord to the findings from the present research, Martín Holguera *et al* found significantly positive association between DXA-derived total, truncal and leg lean mass were significantly related to FEV_1, FVC, PEF (a spirometric indicator of expiratory muscle strength) and $FEF_{25-75\%}$ (an indicator of the small airway patency) (Martín Holguera *et al.*, 2017). Also, the PROOF study (Costes *et al.*, 2016) provided the evidence that truncal lean mass was a predictor of respiratory muscle strength (measured as the maximum inspiratory pressure (MIP)) in older women.

These observations suggest that the effect of body composition on pulmonary function is exerted via segment-specific mechanisms that involve respiratory muscle function, lung compliance and peripheral airway dynamics. The potential cross-link between appendicular adiposity, metabolic homeostasis and inflammatory markers requires further research.

Although the present study was underpowered for subgroup analysis, some observations are worth mentioning.

In men, body shape and body size both showed significant negative correlations with FEV_1 and FVC but not FEV_1 /FVC, denoting proportional changes in FEV_1 and FVC per changes in body mass (BMI and New BMI) and the body size adjusted surrogate measures of fatness (WHR, WHtR, and ABSI). A similar yet non-significant trend was observed in women, perhaps because of the sex disparities in the anatomy and physiology of respiratory tract as well as the varied regional distribution of fat depots and differential proportionality of fat and lean compartments in male and female subjects. Sex-dependent association between lung function and anthropometric measures have been reported previously in the population-based cross-sectional and prospective studies (Chen *et al.*, 2012; Karastergiou *et al.*, 2012; Fenger *et al.*, 2014). Another factor that can contribute to these associations is the baseline adiposity status. Although the SPs were not stratified by their fatness status, several studies have underscored the greater impact of body mass changes on the respiratory capacity and airflow among obese individuals (Thyagarajan *et al.*, 2008; Santamaria *et al.*, 2011; Fenger *et al.*, 2014). It is worth mentioning that WC would not relate significantly to spirometric indices unless it was adjusted for the variations in height, hip circumference, or BMI. This underlies the confounding effect of body size on the associations between WC, as a proxy measure of the abdominal adiposity, and various outcomes (Malara, Anna and Tkaczyk, 2015; Ashwell and Gibson, 2016). This is in line with the results of the British Regional Heart Study (Wannamethee, Shaper and Whincup, 2005) and the Humboldt Study (Chen *et al.*, 2007) which demonstrated BMI or height-adjusted inverse associations between adiposity (WHR and WC) and spirometric parameters (FEV_1 and FVC) in healthy adult males. While in men, measures of central adiposity correlated more strongly with FEV_1 and FVC, measures of general adiposity showed closer relationships with these spirometric parameters in women. A similar trend of relationship was observed for the BIA-derived measures of fatness in both sexes. In contrast, the observed relationships between BIA-estimated leanness/muscularity and lung function in men and women were in opposite directions.

Whereas female SPs with higher levels of total and segmental leanness/muscularity had lower FEV_1 and FVC, male SPs with larger quantities of total and segmental

lean/muscle mass had higher FEV_1 and FVC. Interestingly, the only significant relationships were between FEV_1 and appendicular (particularly lower limb) fat and skeletal muscle mass in men. (). This means that the striated muscle in legs may influence the airway resistance and the expiratory flow rate more significantly than lung compliance and vital capacity. it is worth noting that, both sets of segmental body compositions were equally related to FEV_1 and FVC albeit in the opposite directions. Thus, ameliorating effects of leg muscles appear to be counteracted by comparably deteriorating effects of adipose tissue in lower extremities. Equal but oppositely directed associations of fat and lean compartments with spirometric parameters have been observed in healthy adults. In a study of Brazilian birth cohorts, %FM and %FFM determined by the BODPOD or DEXA had quantitatively similar multivariable-adjusted effects on FEV_1 at 18 and 30 years though in reverse directions (De Oliveira *et al.*, 2016). Besides, DXA-measured %TFM, %AFM and % LFM were significantly negative predictors of FEV_1 in their study. However, the researchers did not investigate the contribution of segmental lean mass to pulmonary function. Leg lean mass has been found to be a significant predictor of FEV_1 and FVC in healthy male and female Caucasians (Martín Holguera *et al.*, 2017) and Asians (Lim *et al.*, 2011). It is also related to handgrip strength which has been identified as a positive predictor of FEV_1 and FVC in healthy adults (Lazarus *et al.*, 1998; Sillanpää *et al.*, 2014).

The finding of non-significant and similarly directed relationships of lean and fat compartments with FEV_1 and FVC in female SPs of the present study can be partially attributed to the lower proportion of FFM in them and the smaller effect of female FFM on the IC and subsequently FEV_1 and FVC (Cotes, Chinn and Reed, 2001). Also, the use of absolute values of body composition might have rendered the observed relationships prone to the confounding effect of height. It is not clear why components of muscle mass exhibited negative associations with FEV_1 and FVC in female SPs. This accords with the findings of Sutherland and his colleagues who reported negative correlations between DXA-derived and height-adjusted total and thoracic lean mass and FEV_1 and TLC in young female New Zealanders free of respiratory disorders (Sutherland *et al.*, 2008). This trend disappeared after adjustment for corresponding fat components. In line with the observations in the current research, they found that total and truncal lean mass were positively but not

significantly correlated with spirometric indices in male participants. Similarly, Scott and his co-workers observed that DXA-determined total and segmental fat and lean mass were negative predictors of FEV_1 and FVC in overweight/obese female asthmatics.

There are, however, some conflicting studies which show positive relationships between measures of respiratory function and leanness in women. For instance, Lazarus and colleagues noticed steady increases in FVC across quintiles of FFM (estimated from skinfold-thickness) in male and female subjects participating in the 1990 Pilot Survey of the Fitness of Australians which reached significance level after adjustment for body fat (Lazarus *et al.*, 1998). One reason could be that muscle bulk is not fully represented by DXA and probably BIA in women. Another possibility could be the greater accumulation of inter or intra-muscular fat or muscle-specific secretion of substances that act upon lung tissue (Sood *et al.*, 2011).

With respect to fat components, differential distribution and function of the adipose tissue, anatomical and physiological dissimilarities of the pulmonary structures, and sex-specific metabolic profile of (Chen *et al.*, 2012; Karastergiou *et al.*, 2012) may explain the observed weaker spirometric correlations.

When the absolute measures of fat and lean mass were replaced by the stature-adjusted indices, total fat-free mass as well as truncal and appendicular muscle mass retained their significant associations with FEV_1 and $FEF_{25-75\%}$, independent of the corresponding fat components in the entire population of study, controlling for demographic, anthropometric, BP and grip variables. This is in concordance with the results of previous studies which showed independently significant associations of depleted FFMI with the severity of COPD (Tkacova *et al.*, 2011; Grydeland *et al.*, 2012) as well as the regional loss of stature-normalised leg and trunk lean mass indices with the risk of asthma (Beckett *et al.*, 2010) and the severity of CF (Bolton *et al.*, 2003). However, none of the BIA-estimated measures of leanness/muscularity showed significant associations with FVC. Thus, it could be speculated that the effect of lean/muscle compartments may be primarily exerted on the airflow and the resistance of airways rather than the elasticity and compliance of the respiratory tract.

Another important finding of this research was the significant interaction of height-normalised total and segmental fat and skeletal muscle mass on the variability in the spirometric parameters. To the best of the author's knowledge, this is the first report on the moderating role of the leanness status in the association between fatness and lung function among healthy adults. Whereas the main effects of height-adjusted total and regional fatness on spirometric indices were positive, their interaction with the equivalent lean mass indices imparted negative effects. In SPs with high levels of total fat-free mass and appendicular muscle mass, FEV_1 and $FEF_{25-75\%}$ declined steadily with incremental changes in total and appendicular fat mass. Comparatively, incremental changes in truncal fat mass of SPs with high levels of truncal muscle mass was associated with steady declines in FEV_1 and FVC. As a consequence, total and segmental body composition phenotypes may determine the respiratory pattern of the adults with no clinically apparent lung disease. Whilst individuals with high fat-high lean whole-body composition and/or high fat-high muscle appendicular composition may exhibit obstructive respiration, those with high fat – high muscle truncal composition may experience a restrictive respiratory pattern. Thus, it appears that at the lower range of fatness, total lean mass and appendicular muscle mass exert beneficial effects on the expiratory flow rate and the calibre and resistance of airways in healthy adults. As the accumulation of fat becomes excessive, however, it takes over the striated muscles and acts as the major body compartment determinant of lung function, mainly affecting the lung compliance.

Distinctive contributions of fat and lean compartments to the mechanics of lungs, respiratory performance, ventilatory capacity, and pulmonary function in men and women have been extensively discussed in Chapter 2. However, the combined impact of fat and muscle mass merits further illumination.

As no study has explored these interactive effects yet, it is very difficult to offer plausible explanations for the relationships found in this research. Nevertheless, the findings signify the interplay between fat and lean (especially muscle) compartments of body composition as the independent determinants of pulmonary function. There is an established crosstalk between skeletal muscle and adipose tissue via common IL-6, TNF-α) and tissue-specific myokines (myostatin, IL-8, IL-15, irisin, fibroblast growth factor 21 (FGF21), and myonectin) and adipokines (leptin, adiponectin, resistin, chemerin, visfatin, and monocyte chemotactic protein-1 (MCP-1)) (Li *et*

al., 2017). Moreover, early life experiences may shape the repertoire of adipomyokines during adult life (Joung *et al.*, 2014). These muscle and fat-derived factors are involved in glucose homeostasis, adipogenesis and lipid metabolism, regulation of cardiovascular system, bone turnover, muscle growth and degeneration, immune function and energy balance (Giudice and Taylor, 2017). Therefore, communication between fat and muscle tissue is largely dependent on the complex and incompletely understood interactions across a wide range of adipokines and myokines. It is conceivable that the adipo-myokine profile of the individuals is an important regulator of the balance between their metabolic load and metabolic capacity, manifesting as total and segmental body composition ratios. This may play a major role in metabolism and function of various organs including cardiovascular and respiratory systems.

IL-6 and TNFα have been shown to be significantly correlated with grip strength and SMI in sarcopenic COPD patients (Byun *et al.*, 2017). Compared with normal individuals, levels of these adipo-myokines are also higher in COPD patients regardless of their current smoking status(Gan *et al.*, 2004; Watz *et al.*, 2009). These patients also have higher leptin and lower adiponectin concentrations (Poulain *et al.*, 2008). In fact, the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study discovered a subgroup of COPD patients characterised by a distinct inflammome (elevated CRP, IL-6, IL-8, TNFα and fibrinogen) and adipokinome (increased leptin and decreased adiponectin) who had poor outcomes (Agustí *et al.*, 2012; Faner *et al.*, 2014). This landmark study identified a novel phenotype of COPD characterised by persistent systemic inflammation (≥2 abnormal inflammatory markers, both at baseline and after 1-year follow-up), obesity, and poor clinical outcomes (severe symptoms, worse functional capacity and QoL, higher cardiovascular morbidity and greater non-COPD related death)(Agustí *et al.*, 2012). This biomarker expedition provided solid evidence on the different systemic inflammome (consisted of WBC, CRP, IL-6, IL-8, TNFα and fibrinogen) and adipokine profile (leptin and adiponectin) of this subgroup of COPD patients (Faner *et al.*, 2014).

Elsewhere, improvements in asthma symptoms, spirometric indices and airway hyperresponsiveness of patients has been documented to parallel improvements in markers of non-allergic airway inflammation (reduced bronchoalveolar lavage

(BAL) fluid neutrophil and eosinophil) and adipokine profile (decreased leptin and increased adiponectin levels in BAL fluid and serum) 12 months after bariatric surgery (Dixon, Pratley, *et al.*, 2011). In a similarly designed intervention, at 12-month follow-up, BAL concentration of IL-8 and MCP-1 and TNFα increased while the level of IL-6, IL-8, MCP-1, and TNFα in SAT decreased in women with adult-onset asthma who had undergone bariatric surgery. In addition, leptin and adiponectin level in BAL correlated with their corresponding levels in SAT and VAT, respectively. Because of the impaired function of the alveolar macrophages and decreased levels of bronchoalveolar pro-inflammatory cytokines in obese patients, it has been postulated that peripherally secreted leptin and pro-inflammatory cytokines may impact the pulmonary function of asthmatics via direct and non-inflammatory effects on the AHR and airway remodelling. The role of locally released leptin in the airways of patients with late-onset asthma has yet to be deciphered (Sideleva *et al.*, 2012)

As leptin, adiponectin and their specific receptors are expressed in airway epithelium (Holguin *et al.*, 2011), alterations in body composition ratio may affect trafficking and actions of these adipokines in respiratory tract. Although the studies on the associations between adipokines and lung disease are inconsistent and sometimes contradictory, there is evidence that they should be linked via several inflammatory and non-inflammatory mechanisms (Sood, 2011). In vitro studies show that leptin stimulates TNFα, MCP-1, and IL-6 production by adipocytes. It also modulates T-cell responses, angiogenesis, and vascular permeability and epithelial cell proliferation in lung parenchyma and, possibly airway remodelling (Shin *et al.*, 2008). Greater bronchial expression of leptin in COPD patients correlates negatively with unadjusted FEV_1 and FEV_1/FVC ratio. High serum leptin levels also increased the risk of asthma in premenopausal women (Sood, Ford and Camargo, 2006). Furthermore, Holguin *et al.*, observed that overweight or obese adults had greater leptin levels in the BAL than lean asthmatic or control groups. Besides, plasma leptin level was higher in overweight or obese asthmatics than BMI-matched controls (Holguin *et al.*, 2011).

Conversely, adiponectin suppresses the production of inflammatory TNFα, IL-6, and vascular cell adhesion molecules while it stimulates the synthesis of anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist(Wolf *et al.*, 2004).

Although unexplored in humans, adiponectin deficiency may result in uncontrolled production of TNFα and matrix metalloproteinases (MMPs) by the alveolar macrophages, leading to emphysematous changes in animals. Adiponectin deficiency also promotes airway inflammation, alveolar smooth muscle proliferation and vascular remodelling (Summer *et al.*, 2008; Medoff *et al.*, 2009). Lower unadjusted serum adiponectin concentration has also been reported in asthmatic women and the BMI-adjusted prevalence of asthma is lower in premenopausal women with high serum adiponectin concentration (Sood *et al.*, 2008). There is, however, conflicting evidence that suggests adiponectin may act as a proinflammatory factor in bronchoalveolar tree, in the individuals with airflow limitation (Miller *et al.*, 2009). In the COPDGene cohort, increased plasma adiponectin level was significantly associated with reduced FVC and FEV_1, decreased post-bronchodilator changes in the percentage predicted value of FEV_1, lower BMI, and CT-assessed emphysema among middle-aged current/ex-smoker adults with stable COPD (Carolan *et al.*, 2013). Paradoxically, high adiponectin level is associated with lower rate of metabolic syndrome and adverse cardiovascular outcomes in individuals with COPD (Minas *et al.*, 2011; Yoon *et al.*, 2012). This discrepancy can be explained by distinct phenotypes of COPD. While undernourished individuals (with higher adiponectin and lower leptin concentrations) have more severe phenotypes and higher risk of short-term death, obese patients with early-stage presentations (and higher leptin to adiponectin ratio) experience a less aggressive clinical course with more frequent cardiovascular comorbidities and higher risk of long-term death (time differential hypothesis) (Divo *et al.*, 2014). Interestingly, in the COPD Quantification by Computed Tomography, Biomarkers, and Quality of Life (CBQ) cohort study, increased adiponectin, decreased leptin and low leptin/adiponectin ratio were significant predictors of rapid annual decline in FEV_1 in the individuals with airflow limitation (Suzuki *et al.*, 2014).

These lines of data underscore the complex relationship between body composition, adipomyokines, lung function, and the clinical picture of pulmonary disease. Nevertheless, the role of insulin-related signalling pathways in these intricate relationships should not be forgotten.

The present study identified a moderating role for the skeletal muscle tissue in the specific associations of whole-body and segmental adiposity with dynamic lung function. It used a very robust quantitative statistical method to specify the absolute changes in spirometric parameters per changes in total and segmental fatness over continuous range of lean or muscle mass. The, recommended procedures for the assessment of body composition and spirometry were also carefully followed to reduce random and systematic error, improving the precision and the accuracy of the measurements. Importantly, the analyses were conducted on the absolute values of the spirometric readings instead of the percentage of the predicted values which have been shown to be non-accurate indicators of abnormal lung function in adults. Furthermore, the comparison of individual spirometric recordings to the reference values was based on the ATS/ERS endorsed spline-smoothed prediction equations proposed by the Global Lung Function Initiative (GLI) to capture the non-linear association of these parameters with age, height and sex. Spirometric measurements were additionally expressed as Z-scores to improve the accuracy and interpretability of the results. For the first time, the current study provided some evidence on the potential implication of body composition phenotyping in the pulmonary assessment of healthy adults. However, it is unclear whether these effects would be applicable to patients with respiratory problems. Also, majority of the participants in this study were young or middle age, non-smokers, physically active and in the mid-range of fatness or leanness. Again, cross-sectional design, small sample size, the use of BIA-estimated measures of fat and skeletal muscle mass, and lack of metabolic, inflammatory, and dietary data limit the accuracy and generalisability of the findings. Since predictive models only included one set of body composition compartments at a time, the contribution of other two sets of compartments to the observed associations cannot be ruled out. For example, in the regression models exploring the effect of truncal fat-muscle phenotypes on spirometric indices was not controlled for the total fat–lean or appendicular fat-muscle phenotypes. Moreover, the influence of metabolic homeostasis (indicated by total fat to fat-free mass or truncal fat to appendicular muscle mass ratios) on respiratory performance was not directly examined. The intricate communication between adipose and skeletal muscle tissues using the appropriate biomarkers (e.g., adipokines or myokines) or the presence of inter- or intramuscular fat were not investigated in this study. The effect of other components of lean mass on the spirometric parameters could have

shed more light on the link between body composition and lung function. Optimally, direct measures of resistance, compliance, elasticity, and reactivity of the respiratory tract could have been used in conjunction with the systemic and intrapulmonary concentration of adipomyokines, and inflammatory markers.

Nonetheless, this preliminary research may be a starting point for large-scale clinical studies on the interplay of adipose, striated muscle, bone and lung tissues and the cross-sectional and longitudinal reciprocal connection between metabolic balance and respiratory function, with special focus on obesity, sarcopenia and bone loss.

Chapter 7

Body Composition Phenotypes and Lung Function by Blood Pressure and Muscle Strength

To investigate the effect of metabolic load-metabolic capacity balance on lung function, measures of fat and lean compartments were composited as FM/FFM and TFM/ASM ratios. The former ratio was used to represent whole-body load-capacity model while the latter ratio was used to indicate segmental load-capacity model. Then, moderation analyses were carried out in the PROCESS to probe the modifying effect of systemic pressure as well as isometric grip strength on the association between spirometric indices and body composition phenotypes. For each spirometric parameter, distinct heteroscedasticity consistent OLS regression models adjusted for age, sex, ethnicity, height, NC, CC and TC were designed. FM/FFM and TFM/ASM ratios were entered separately in the corresponding models as the independent variables. For each model, DBP, SBP and Grip strength were added alternatively as the moderator. When one of these variables was defined as the moderator, the other two were treated as covariates. The conditional effects of the body composition phenotypes on spirometric parameters were plotted against low, medium and high levels of the moderators.

Results

7.1 Relative body composition and lung function by blood pressure

Variations in FEV_1 was predicted significantly by FM/FFM ratio at low levels of DBP with significant associations (Table 7.1) detectable in SPs with DBP<72.39mmHg. At lower values of DBP (16^{th} percentile), 0.1point increment in FM/FFM ratio was associated with approximately 100ml decrement in FEV_1 *(*β=-.104; 95%CI (-.163, -.445), p<0.01). Similarly, significant influence of FM/FFM on

FVC was exerted only in the lower range of DBP values (<65.66mmHg). At 16th percentile of DBP, FVC dropped by 127ml per 0.1point increase in FM/FFM. Comparatively, FM/FFM ratio was a significant predictor of $FEF_{25-75\%}$ at all three levels of DBP, with significant associations detectable in SPs with DBP<75.72mmHg and >86.31mmHg. At lower values of DBP (16th percentile), 0.1point increment in FM/FFM ratio was associated with 357ml/s decrement in $FEF_{25-75\%}$ *(*β=-.357; 95%CI (-.47, -.24), p<0.001). Equal changes in FM/FFM also predicted about 120ml/s decrease in $FEF_{25-75\%}$ at 50th percentile of DBP *(*β=-.119; 95%CI (-.22, -.02), p<0.05). On the contrary, $FEF_{25-75\%}$ increased by 164ml/s per 0.1point increment in FM/FFM *(*β=-.164; 95%CI (.213, .307), p<0.05) at 84th percentile of DBP. None of the spirometric indices showed significant relationship with segmental relative body composition (TFM/ASM) either directly or conditionally via interaction with DBP.

By contrast, SBP moderated the influence of segmental relative body composition on pulmonary function (Table 7.2). TFM/ASM contributed significantly to the prediction of FEV_1 in the middle and high range of SBP values (> 111.22mmHg). At 50th percentile of SBP, each 0.1point increase in TFM/ASM was associated with 69.8ml decrease in FEV_1*(*β=-.069; 95%CI (-.135, -.005), p<0.05) while equal rise in TFM/ASM predicted 163ml fall in FEV_1*(*β=-.163; 95%CI (-.252, -.074), p<0.001). Significant interaction between segmental relative body composition and SBP was also observed for $FEF_{25-75\%}$ which declined by 148ml/s *(*β=-.163; 95%CI (-.266, -.030), p<0.05) and 349ml/s *(*β=-.349; 95%CI (-.504, -.194), p<0.001) per 0.1point increment in TFM/ASM at middle (50th percentile) and high (84th percentile) levels of SBP, respectively. Nonetheless, SBP and TFM/ASM did not have a significant interaction effect on FVC. Moreover, none of the spirometric parameters were significantly associated with FM/FFM at any level of SBP.

Table 7.1 Relative total body composition and lung function by diastolic blood pressure

Spirometric parameter	FM/FFM by DBP percentile		
	16th percentile (64.5mmHg)	50th percentile (75mmHg)	84th percentile (87.5mmHg)
FEV_1 (L)	-.104** (-.163, -.044)	-.042 (-.103, .018)	.031 (-.063, .126)
FVC (L)	-.127* (-.249, -.006)	-.070 (-199, .058)	-.002 (-.165, .161)
$FEF_{25-75\%}$ (L/s)	-.357*** (-.469, -.244)	-.119* (.220, -.018)	.164* (.021, .307)

Values are presented as β(95% CI) for FM/FFM

**p<0.05; **p<0.01; ***p<0.001*

OLS regression models were adjusted for age, sex, height, ethnicity, neck circumference, calf circumference, and thigh circumference.

FM/FFM: fat mass to fat-free mass ratio; DBP: diastolic blood pressure; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

Table 7.2 Relative segmental body composition and lung function by systolic blood pressure

Spirometric parameter	TFM/ASM by SBP percentile		
	16th percentile (102 mmHg)	50th percentile (112 mmHg)	84th percentile (126 mmHg)
FEV_1 (L)	-.002 (-.070, .064)	-.069* (-.134, -.005)	-.163*** (-.252, -.074)
$FEF_{25-75\%}$ (L/s)	.007 (-.121, .136)	-.148* (-.266, -.030)	-.349*** (-.504, -.194)

Values are presented as β(95% CI) for FM/FFM

FVC did not associate significantly with TFM/ASM at any level of SBP

**p<0.05; **p<0.01; ***p<0.001*

OLS regression models were adjusted for age, sex, height, ethnicity, neck circumference, calf circumference, and thigh circumference.

TFM/ASM: truncal fat mass to appendicular skeletal muscle mass; SBP: systolic blood pressure; FEV_1: forced expiratory volume in 1 s; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

7.2 Relative body composition and lung function by muscle strength

To explore the influence of muscle strength on the association between whole-body and segmental metabolic homeostasis and pulmonary function, the isometric grip strength of the SPs was used as a moderating factor in the adjusted linear regression models, with total fat to fat-free mass or truncal fat to appendicular muscle mass ratios set as the predictive variables.

The moderation analysis demonstrated that the impact of total body composition phenotype on all three measures of lung function was significantly dependent on the strength of grip force (Figure 7.1). In SPs with hand grips at the middle (33kg) and high levels of strength (46kg), FEV_1 decreased respectively by 66ml (β=-.065; 95%*CI*(-.129, -.002), $p<0.05$) and 273ml (β=-.273; 95%*CI*(-.367, -.179) , $p<0.001$) per 0.1point increment in FM/FFM. The association between FM/FFM and FVC also became significant when grip strength exceeded 35.31kg, with each 0.1point increase in FM/FFM significantly predicting 331ml fall in FVC (β=-.331; 95%*CI*(-.552, -.111), $p<0.01$) at high level of grip strength (84^{th} percentile). $FEF_{25-75\%}$ also dropped by 257ml (β=-.257; 95%*CI* (-.384, -.129), $p<0.001$) and 579ml (β=-.579; 95%*CI* (-.768, -.391), $p<0.001$) in the middle (50^{th} percentile) and high (84^{th} percentile) levels of grip strength, respectively.

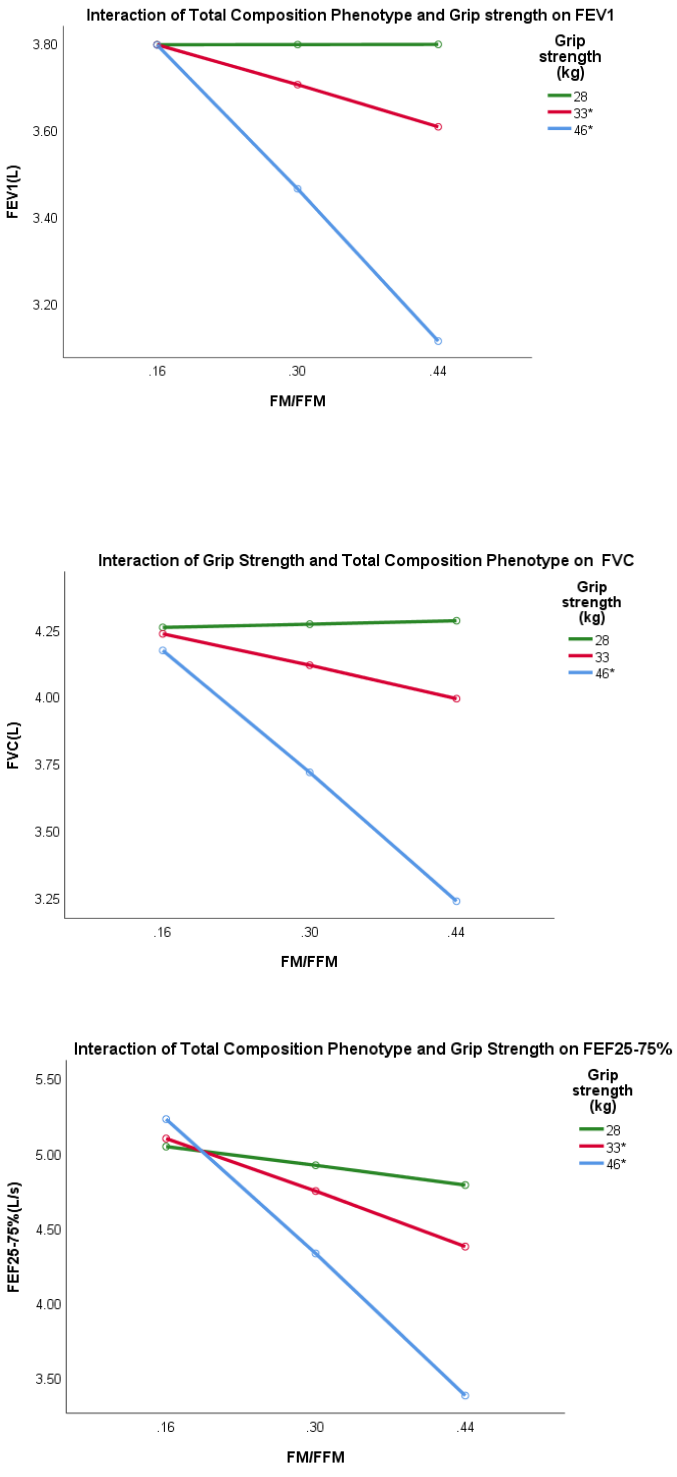


Figure 7.1. Moderating effect of grip strength on FM/FFM relationship with a) FEV_1, b) FVC and c) $FEF_{25-75\%}$.

**grip strength level with significant effect of FM/FFM on spirometric parameters.*

Grip strength levels represent 16^{th}, 50^{th} and 84^{th} percentiles.

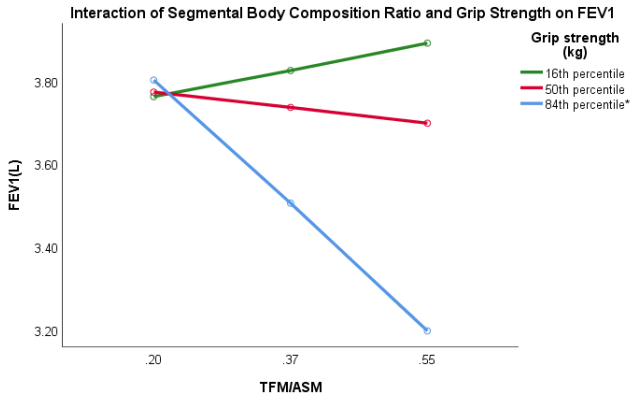
FM/FFM: fat mass to fat-free ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

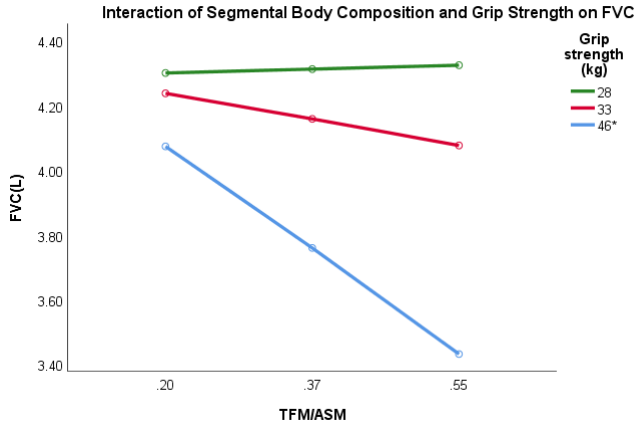
Therefore, the effect of whole-body metabolic overload on reducing $FEV_{1,}$ FVC and $FEF_{25-75\%}$ was steadily augmented by incremental changes in grip strength. SPs with greater distal muscle strength had significantly lower spirometric recordings at any given quantity of total fat to fat-free mass ratio. Since all three indices declined, it could be conjectured that metabolic imbalance in otherwise healthy adults with stronger grips may primarily target the resistance and calibre of the bronchoalveolar tree rather than the compliance and elasticity of the lung.

Similarly, isometric grip force moderated the influence of segmental metabolic balance on $FEV_{1,}$ FVC and $FEF_{25-75\%}$ (Figure 7.2). Significant transitions in TFM/ASM- FEV_1 relationship occurred at grip strengths above 35.65kg. At high levels of strength (84^{th} percentile), FEV_1 decrease by 209ml per 0.1point increment in TFM/ASM (β=-.209; 95%*CI* (-.299, -.119), $p<0.001$). In a similar fashion, FVC declined by 179ml (β=-.179; 95%*CI* (-.310, -048.), $p<0.01$) at 84^{th} percentile of grip strength. Also, $FEF_{25-75\%}$ fell by 419 ml/s per 0.1point rise in TFM/ASM (β=-.419; 95%CI (-.582, -.256), $p<0.001$) in SPs with stronger grips (84^{th} percentile).

Thus, deleterious impact of excessive metabolic load on respiratory performance at the segmental level emerged as a function of the distal muscle strength, suggesting that healthy adults with stronger grips may have lower $FEV_{1,}$ FVC and $FEF_{25-75\%}$ at any given quantity of truncal fat to appendicular muscle ratio.

As a result, metabolic imbalance at whole-body and segmental levels, by limiting vital capacity and flow rate, may create an obstructive respiratory pattern in adults with greater muscle strength.





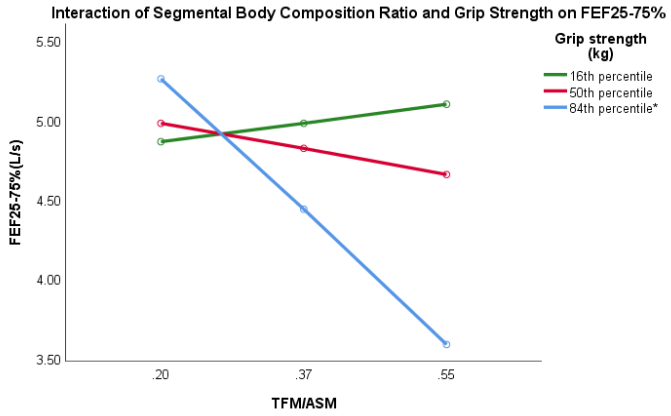


Figure 7.2. Moderating effect of grip strength on TFM/ASM relationship with a) FEV_1, b) FVC and c) $FEF_{25-75\%}$.

**grip strength level with significant effect of FM/FFM on spirometric parameters.*

Grip strength levels represent 16th, 50th and 84th percentiles.

TFM/ASM: truncal fat mass to appendicular skeletal muscle ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

Discussion

The present study elucidated that the combined impact of total as well as regional fat and skeletal muscle mass on the respiratory capacity was modified by the systemic blood pressure and the isometric grip strength.

7.3 Modifying roles of blood pressure in the association between body composition phenotype and lung function

A very interesting finding of the present study was the faceted connection between systemic blood pressure, body composition and lung function. While diastolic pressure moderated the negative influence of whole-body metabolic overload on all spirometric indices, systolic pressure was a moderator of the deleterious impact exerted by segmental metabolic overload over lung function. Increased FM/FFM ratio as an index of whole-body metabolic load could predict diminished FEV_1, FVC and $FEF_{25-75\%}$ at lower DBP values. By contrast, increased TFM/ASM ratio, as an index of segmental metabolic load, predicted decreased FEV_1 and $FEF_{25-75\%}$ at higher levels of SBP. Although the underlying mechanisms are not clear, it can be speculated that earlier in the process of metabolic imbalance, when concomitant physiologic derangements have contributed to the increases in systolic pressure, moderate to small-sized airways are narrowed and bronchial smooth muscles are hyperresponsive, increasing airway resistance especially at high gas flow rates during forced expiration. This may limit FEV_1 and mid-expiratory flow rate without impairing vital capacity. With the progression of the imbalance to the point where diastolic pressure is negatively affected by the stiffened arteries, elastic recoil and respiratory compliance are impaired, reducing vital capacity and FVC. This hypothesis may be supported if variations in the corresponding spirometric indices can be predicted from changes in SBP and/or DBP. This speculative association will be tested in the next two chapters.

It is worthwhile to stress the importance of the local regulators of regional vascular resistance, *i.e.*, metabolic activity, myogenic mechanisms, and flow-mediated dilation of peripheral vessels (that adjusts the rate of diastolic runoff in the vasculature) as well as the elasticity of large arteries (that influences the afterload

and systolic output) in controlling arterial pressure (Magder, 2014). Several studies have demonstrated a J-shaped relationship between DBP and carotid intimal thickness, progression of atherosclerotic plaques and cardiovascular events, especially in hypertensive or elderly population (Farnett *et al.*, 1991; Bots *et al.*, 1996; Somes *et al.*, 1999). It has been hypothesised that central arterial stiffness may lower DBP and subsequently impair coronary blood flow and LV function (Cruickshank, Thorp and Zacharias, 1987; Sleight, 1988). SBP is also dependent on the stiffness of central arteries, stroke volume, and wave reflections from peripheral arteries. LV mass and contractility, in turn, are affected by long-term alterations in SBP. Thus, endothelial dysfunction, intimal thickening and atherosclerosis may be the factors underlying this phenomenon (Witteman *et al.*, 1994).

The contribution of fat and lean compartments to the regulation of systemic blood pressure has been extensively discussed in the literature review. The relevance of metabolic load-capacity balance to BP has been emphasised in the Avon Longitudinal Study of Parents and Children (ALSPAC) which illustrated positive effect of DXA-measured FM/LM ratio and the negative effect of birth weight on DBP, SBP, and the odds for hypertension at 9 years among white European children (Grijalva-eternod, Lawlor and Wells, 2013). Based on the thrifty phenotype hypothesis, metabolically active organs (kidneys, liver, pancreas, vasculature, hypothalamic-pituitary-adrenal axis and sympathetic systems) of individuals with restricted foetal and post-natal growth are not fully equipped to tolerate the metabolic load imposed on them by the environmental factors and the linear growth during childhood and early adulthood, predisposing these individuals to metabolic syndrome, hypertension and type 2 diabetes later in life (Hales and Barker, 2001). In addition, height, fat mass, BP, and (more strongly) lean mass are independently significant determinant of LV mass in children and adolescents (Daniels *et al.*, 1995)(Janz, Burns and Mahoney, 1995)(Urbina *et al.*, 1995). In this regard, low ASM/VFA ratio emerged as an independent risk factor for metabolic syndrome and arterial stiffness (measured by brachial artery pulse wave velocity(baPWV)) in the KSOS. Furthermore, the age and sex-adjusted favourable effect of a high ASM/VFA ratio on DBP, SBP, baPWV, fasting glucose, and HDL cholesterol contrasted the adverse effect of a high ASMI on these entities (Kim *et al.*, 2011). A separate analysis of the data from the KSOS also demonstrated the multivariable-adjusted

association between higher levels of visceral fat to thigh muscle area (VFA/TMA) ratio and unfavourable profile of metabolic syndrome components (Lim *et al.*, 2010). As reviewed in chapter 2, the individual links between fat and lean compartments, lung function, atherosclerosis, arterial stiffening, insulin resistance, and inflammation have been repeatedly underscored in a large battery of studies. Thus, this is conjecturable that components of total and segmental body composition exert interactive inflammatory, endocrine and metabolic effects on the development and function of respiratory system through or in parallel to the static and dynamic changes in the elements of cardiovascular system. This possibility will be discussed in more details in the next chapter.

7.4 Moderation of total body composition-lung function relationship by isometric grip strength

The present research also shed light on the moderating role of muscle strength in the association between metabolic homeostasis and pulmonary function. FM/FFM ratio was a significantly negative predictor of all three spirometric parameters, *i.e.*, FEV_1, FVC and $FEF_{25-75\%}$ at high levels of isometric grip strength. In other words, SPs with the largest metabolic load and strongest grips had the lowest vital capacity and the expiratory flow rate as compared to other SPs, controlling for demographic, anthropometric and BP characteristics. Handgrip force, as an indicator of peripheral muscle strength, is a surrogate marker of respiratory muscle strength, a strong correlate of skeletal muscle mass and an independent predictor of physical functioning and clinical outcomes. It also correlates with maximal expiratory pressure (MEP) and more significantly maximal inspiratory pressure (MIP) in young and older healthy populations (Enrighi *et al.*, 1994; Bahat *et al.*, 2014; Efstathiou, Mavrou and Grigoriadis, 2016). Recently, a dose-dependent positive association was found between handgrip strength and pulmonary function in community dwelling older Korean women (Son *et al.*, 2018). In this secondary analysis of KNHANES, women in the lowest quartile of hand-flexor strength were respectively 2.6 and 3.5 times more likely to have impaired FEV_1 and FVC (LLN values) as compared to those with stronger grips. Therefore, it can be conjectured that the effect of body

composition ratio on spirometric parameters is partially mediated via contractile force of inspiratory and (less strongly) expiratory muscles.

Thus, the increased grip force, as a surrogate measure of respiratory muscle strength, may represent higher skeletal muscle mass and faster expiratory flow rate. In this group of individuals, elevated whole-body and segmental body composition ratios could be indicative of highly accumulated fat both totally and truncally. This may result in greater declines in vital capacity and flow rate as compared to individuals with weaker grip strength and probably lower skeletal muscle mass whose elevated body composition ratios would represent quantitatively smaller fat depots.

This possibility could have been explored better if the absolute values of total and truncal fat mass as well as total fat-free mass and appendicular muscle mass had been included in the predictive models as separate variables.

With regard to the handgrip measurement, the handheld dynamometer (Takei) used in this study may underestimate the grip force in the dominant and non-dominant hands of male and female adults as compared to Jamar dynamometer which is considered to be the criterion standard for the assessment handgrip strength (Amaral, Mancini and Novo Júnior, 2012). This limitation together with the standing position of SPs during dynamometry could have entered some degrees of systematic and random errors in the analysis; however, the compliance with the standard protocols would have reduced these errors. Limitations addressed in previous chapters should not be forgotten too.

Chapter 8

Systemic Blood Pressure and Lung Function

To test the hypothesis of the interrelation between systemic blood pressure and lung function, the main effects of systolic, diastolic and mean arterial blood pressure on spirometric parameters was analysed in the heteroscedasticity-corrected linear regression models adjusted for age, sex, ethnicity, height, NC, CC, TC, grip strength, FFMI and FMI.

To create standardised coefficients of determination, Z-scores of the explanatory and outcome variables were calculated. Then, Z-score were included in the regression models instead of the absolute values.

The conditional effect of systemic BP on spirometric indices was probed using moderation analysis. In the models pertinent to each spirometric index, DBP, SBP and MAP were separately included as main predictors while FM/FFM ratio was defined as the moderator. The effect of main predictors on each spirometric parameter was plotted against three levels (16^{th}, 50^{th} and 84^{th} percentile) of FM/FFM ratio.

Results

8.1 Systemic blood pressure as a predictor of pulmonary function

Models incorporating DBP and SBP significantly predicted variability in FEV_1 (R^2=.76, .74, p<0.001), FVC (R^2=.73, .72, p<0.001) and $FEF_{25-75\%}$ (R^2=.32, .33, p<0.001).

As presented in Table 8.1, DBP and SBP demonstrated significantly negative associations with FEV_1 (standardised β=-.24, -.16, p<0.001), FVC (standardised β=-.15, -.12, p<0.001), and $FEF_{25-75\%}$ (standardised β=-.30, p<0.001 and -.26, p<0.01),

respectively. This may be indication of increased airway resistance and airflow limitation with potentially collapsible small airways in healthy adults with higher systolic and/or diastolic pressures who are free of clinically apparent respiratory disease.

In the DBP-included models, sex, ethnicity, height and grip strength were the significant covariates of FEV_1 and FVC. FMI contributed significantly to the variation in FEV_1 whereas TC, CC and FFMI were significant contributors to FVC prediction. Age, height, TC, CC and grip strength were significant predictors of $FEF_{25-75\%}$. Neither FMI nor FFMI displayed significant associations though. For SBP models, however, FMI significantly and negatively predicted the changes in FEV_1 (standardised β=-.16, p<0.05), FVC (standardised β=-.16, p<0.05), and $FEF_{25-75\%}$ (standardised β=-.20, p<0.001). In contrast, FFMI acted as a significant predictor only for FEV_1 (standardised β=.16, p<0.05). Therefore, fat and lean body compartments had distinctive effects on pulmonary function.

Table 8.1 Systemic blood pressure as the predictor of lung function

Spirometric parameter	Systemic blood pressure (mmHg)					
	SBP			DBP		
	Unstandardised β(*SE*)	Standardised β	*p*-value	Unstandardised β(*SE*)	Standardised β	*p*-value
FEV_1 (L)	-.011(±.002)	-.158	<.001	-.019(.004)	-.246	<.001
FVC (L)	-.011(±.003)	-.120	<.001	-.022(004)	-.158	<.001
$FEF_{25-75\%}$ (L/s)	-.023(±.004)	-.259	<.001	-.023(007)	-.305	.002

Multiple linear regression models were adjusted for age, sex, height, ethnicity, neck circumference, calf circumference, thigh circumference, grip strength, FFMI and FMI.

DBP: diastolic pressure; SBP: systolic pressure; FEV_1: forced expiratory volume in 1 s; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

8.2 Moderating effect of body composition phenotype on the relationship between systemic blood pressure and lung function

To clarify the combined influence of fat and lean compartments on the link between haemodynamic status and respiratory capacity, total and segmental body composition ratios were included as moderators in the prediction models.

DBP but not SBP predicted the variations in FEV_1 (R^2=.76, p<0.001), FVC (R^2=.72, p<0.001) and $FEF_{25-75\%}$ (R^2=.42, p<0.001) significantly. Sex, height, TC and grip strength were the significant covariates for all three spirometric measures while ethnicity associated significantly with FEV_1 and FVC. In addition, NC and CC were significant predictors of FVC.

DBP had a significantly negative effect on FVC across all levels of FM/FFM and on FEV_1 at low and mid-range of FM/FFM (Table 8.2). The slope of association was steeper (Figure 8.1) at lower values (16^{th} percentile) of FM/FFM compared with middle (50^{th} percentile) and higher (84^{th} percentile) values. Significant associations between DBP and FEV_1 was observed for FM/FFM values below 0.45 whereas the relationship between DBP and FVC retained significance at FM/FFM values below 0.49.

For each 1mmHg rise in DBP, FEV_1 declined by 35ml (β=-.035, p<0.001), 22ml (β=-.022, p<0.001) and 9ml (β=-.009, p>0.05) at low, mid and high levels of FM/FFM, respectively. In a similar order of interaction, FVC dropped by 37ml (β=-.037, p<0.001), 23ml (β=-.023, p<0.001) and 9ml (β=-.009, p<0.01) per 1mmHg increase in DBP. In comparison, $FEF_{25-75\%}$ was negatively influenced by DBP at low (β=-.059, p<0.001) and middle (β=-.022, p<0.01) levels of FM/FFM whilst it showed positive association at high levels of FM/FFM (β=.019, p<0.05).

Table 8.2 Main and interaction effects of total body composition phenotype and DBP on pulmonary function

Spirometric parameter	Main effect	Interaction with FM/FFM		
	DBP	16th percentile (0.16)	50th percentile (0.30)	84th percentile (0.44)
FEV_1 (L)	-.049*** (-.065, -033)	-.035*** (-.045, -.024)	-.022*** (-.030, -.014)	-.009 (-.017, .000)
FVC (L)	-.052*** (-.075, -.029)	-.037*** (-.053, -.021)	-.023*** (-.034, -.013)	-.009* (-.019, -.000)
$FEF_{25-75\%}$ (L/s)	-.104*** (-.128, -080)	-.059*** (-.075, -.043)	-.021** (-.034, -.008)	.019* (.002, .036)

Values are presented as β(95% CI)

**p<0.05; **p<0.01; ***p<0.001*

OLS regression models were adjusted for age, sex, height, ethnicity, neck circumference, calf circumference, thigh circumference and grip strength.

DBP: diastolic pressure; FM/FFM: fat mass to fat-free mass ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

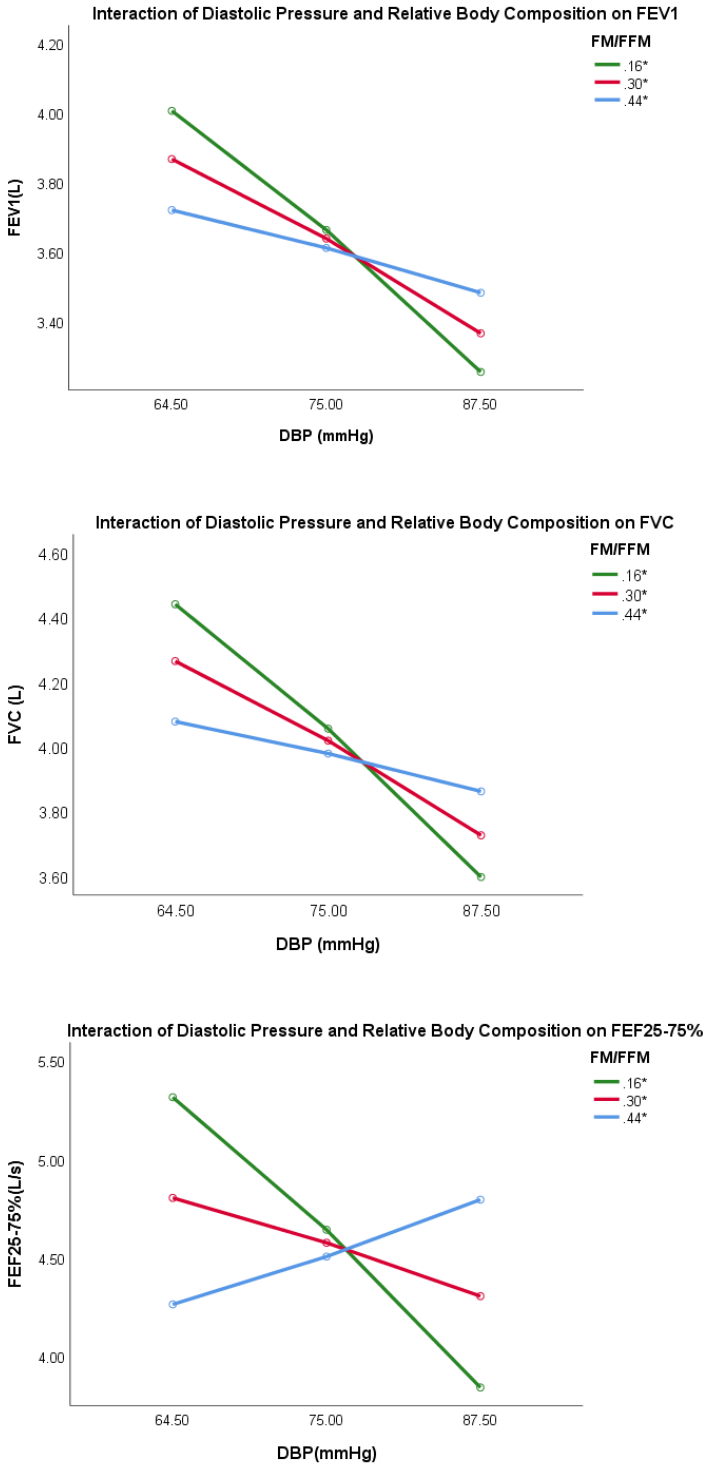


Figure 8.1. Moderating effect of whole-body composition phenotype on DBP relationship with a) FEV_1, b) FVC and c) $FEF_{25-75\%}$.

FM/FFM values represent 16th, 50th and 84th percentiles.

**FM/FFM level with significant effect of DBP on spirometric parameters.*

DBP: diastolic pressure; FM/FFM: fat mass to fat-free mass ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

Despite non-significant main effect of SBP on parameters of lung function, the associations of SBP with FEV_1 and FVC became significant at FM/FFM values greater than 0.20 and 0.27, respectively. In SPs with mid (*0.30 to 0.44)* and high (≥0.44)-range FM/FFM, FEV_1 decreased respectively by 12ml (β=-.035, p<0.001; 95%CI -.018 to -.006) and 20ml (β=-.035, p<0.001; 95%CI -.027 to -.012) per 1mmHg rise in SBP. The equivalent increase in SBP also predicted 10ml (β=-.010, p<0.001; 95%CI -.018 to -.002) and 23ml (β=-.035, p<0.001; 95%CI -.032 to -.013) fall in FVC (Figure 8.2).

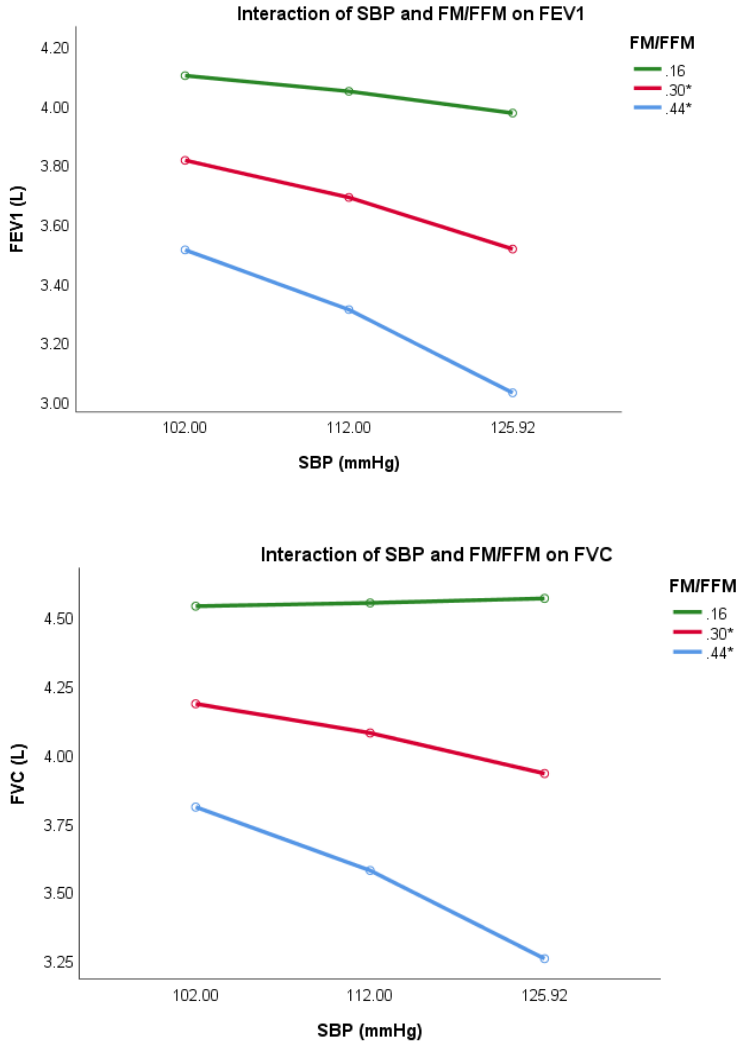


Figure 8.2. Moderating effect of whole-body composition phenotype on SBP relationship with a) FEV_1, b) FVC.

FM/FFM values represent 16th, 50th and 84th percentiles.

**FM/FFM level with significant effect of SBP on spirometric parameters.*

SBP: systolic pressure; FM/FFM: fat mass to fat-free mass ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Thus, in otherwise healthy adults with low to moderate whole-body metabolic burden, FEV_1 and FVC may drop to a larger extent than their metabolically overloaded peers per given increments in diastolic pressure. Oppositely, the inverse association of systolic pressure with FEV_1 and FVC could be of a larger magnitude in otherwise healthy adults with medium to high metabolic overload than those with lower metabolic burden at whole-body level.

Importantly, MAP exhibited significantly negative main effects on all three spirometric indices. FEV_1, FVC and $FEF_{25-75\%}$ decreased by approximately 45ml, 40ml, and 100 ml/s per 1mmHg increment in MAP. Moreover, total body composition phenotype significantly moderated the influence of mean arterial pressure on respiratory capacity. The magnitude of MAP effect on spirometric parameters decreased with continuous increments in FM/FFM ratio. FEV_1, FVC and $FEF_{25-75\%}$ declines per unit increases in MAP were larger (33ml, 31ml and 68ml/s) at low levels (16^{th} percentile) than high levels (84^{th}) of FM/FFM ratio (13ml, 13ml and 11ml) (Table 8.3). Thus, in adults with no clinical respiratory disease and low metabolic load, vital capacity, expiratory flow rate and small airway calibre may decline more significantly than their metabolically overloaded counterparts per incremental changes in mean arterial pressure.

Table 8.3. Main and interaction effects of total body composition phenotype and MAP on pulmonary function

Spirometric parameter	Main effect	Interaction with FM/FFM		
	MAP (mmHg)	16th percentile (0.16)	50th percentile (0.30)	84th percentile (0.44)
FEV_1 (L)	-.044*** (-.061, -027)	-.033*** (-.043, -.022)	-.023*** (-.030, -.017)	-.013*** (-.020, .005)
FVC (L)	-.041*** (-.066, -016)	-.031*** (-.046, -.016)	-.023*** (-.031, -.014)	-.013** (-.022, -.005)
$FEF_{25-75\%}$ (L/s)	-.101*** (-.129, -071)	-.068*** (-.085, -.051)	-.041*** (-.052, -.029)	.011 (-.027, .004)

Values are presented as β(95% CI)

*p<0.05; **p<0.01; ***p<0.001

OLS regression models were adjusted for age, sex, height, ethnicity, neck circumference, calf circumference, thigh circumference and grip strength.

MAP: mean arterial pressure; FM/FFM: fat mass to fat-free mass ratio; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

Discussion

In the present study, diastolic and systolic pressures were inversely associated with all three spirometric indices, independent of age, sex, ethnicity, muscle strength and anthropometric as well as BIA-derived measures of lean and fat mass. The largest effect of DBP and SBP was exerted on FEF_{25-75}, followed by FEV_1, implying that haemodynamic changes underlying the elevated systemic blood pressure can be more closely linked to the alterations in the structure and function of small airways rather than larger proximal airways.

Another notable finding of this study was the emergence of an inverse association between diastolic pressure and dynamic lung function in otherwise healthy adults, particularly in those with low metabolic load at whole-body level.

Hence, the magnitude of decline in FEV_1, FVC and $FEF_{25-75\%}$ per increments in diastolic pressure could be larger when there is a predominance of lean over fat mass. As a result, the contribution of DBP to lung function can be partially attributed to the moderating role of body composition, though there should be other linking mechanisms too.

In contrast, the effect of SBP on FEV_1 and FVC was totally dependent on body composition, losing significance after adjustment for FM/FFM. Moreover, the negative association between respiratory performance and systolic pressure appeared only at mid and high levels of FM/FFM, indicating that individuals with metabolic overload at the whole-body level are more prone to the potentially adverse effects of elevated systolic pressure on their pulmonary function. Thus, it appears that SBP relates to respiratory capacity through mediation of metabolic imbalance.

Predictive value of BP for lung function variations in adults free of respiratory problems has been addressed in a few studies. Adjusting for sex, age, height, weight, education level, smoking, and the history of pulmonary and cardiac diseases, high blood pressure and the use of beta blockers synergistically produced adverse respiratory effects in the participants of the Cooperative Health Research in the Region of Augsburg (KORA) F4 study. Patients who remained hypertensive despite using beta blockers would experience the largest reductions in FEV_1 and FVC as compared to normotensive subjects without taking antihypertensive agents. There

was a significant interaction between sex and raised BP on FVC such that increased BP had a greater negative impact on the vital capacity of men. Also, hypertension and beta blocker use had independently inverse associations with FEV_1 and FVC (Schnabel, Karrasch, *et al.*, 2011). Similar results were reported from the European Community Respiratory Health Survey (ECRHS)-I Erfurt study which estimated 150ml and 190ml reduction in multivariable (sex, age, BMI, education, smoking, and respiratory symptom) adjusted FEV_1 and FVC among subjects with uncontrolled hypertension as compared to normotensive subjects not receiving antihypertensives. It was found, however, that the association between high blood pressure and spirometric indices lost significance when the medication use was added as a separate explanatory variable (Schnabel, Nowak, *et al.*, 2011). Data from the non-institutionalised Icelanders who took part in the Burden of Lung Disease Initiative (BOLD) yielded similar results. Multivariable adjusted FEV_1% and FVC% predicted values were independently and inversely associated with hypertension, BMI and CRP (Margretardottir, Thorleifsson and Gudmundsson, 2012). Again, the associations with FVC% were stronger in male than female subjects. Furthermore, hypertension and increased CRP (>1.27mg/L) demonstrated additive effects on FEV_1% whilst FVC% was lowest in the subjects with simultaneous increases in all three predictors, denoting the contribution of BP, body composition and systemic inflammation to the variability in lung function among adult population. In line with these findings, a cross-sectional analysis of French men without coronary heart disease exhibited significantly inverse association between arterial stiffness and pulmonary function. In this study, FEV_1 and FVC declined respectively by approximately 200ml and 160ml per 2.5 m/s increments in carotid–femoral pulse-wave velocity (cfPWV), accounting for age, height, weight, hypercholesterolaemia, diabetes and hypertension (Zureik *et al.*, 2001). This accords with the inverse association between the mean arterial pressure and $FEV_{1,}$ FVC and $FEF_{25-75\%}$ observed in the current study, indicating that arterial stiffness, more specifically vascular resistance, can be related to the expiratory flow, vital capacity and small airway calibre.

The underpinning of the observed association between vascular and respiratory systems is poorly understood but a number of explanations have been offered. One possible reason could be the interstitial pulmonary oedema caused by left ventricular

dysfunction and elevated pulmonary artery pressure subsequent to persistently increased systemic BP and afterload. Fluid accumulation in lung parenchyma reduces lung compliance and functional residual capacity, reducing FEV_1 and FVC. In fact, the Cardiovascular Health Study (CHS) provided evidence of the independent deteriorating influence of left ventricular (LV) enlargement, especially the end-diastolic posterior wall LV thickness, on (age, height, and waist girth) adjusted FEV_1 and FVC among non-smoking elderly population without pulmonary disease. In addition, systolic hypertension (reflecting augmented arterial stiffness) was an independent predictor of FVC decline (Enright *et al.*, 1995). Respiratory flow is limited further by the bronchoconstrictive effects of beta-blockers commonly prescribed to treat high BP (Doshan *et al.*, 1986). Other blood pressure medications such angiotensin converting enzyme inhibitors (ACEI) and calcium channel blockers are also known for their respiratory side effects (Vegter and de Jong-van den Berg, 2010). The contributory role of smoking seems unlikely because the models operated in these studies controlled for smoking and the associations also existed in non-smokers. As dissected earlier, fat and lean compartments can significantly modify cardiovascular and respiratory functions, thereby linking the altered haemodynamics of the vascular bed to the impairments in the respiratory capacity. In this respect, it had been suggested that decreased FEV_1 and FVC could be physiologic phenotypes of centripetal obesity and physical inactivity (Weiss, 1991) as the impaired lung function was related to lower HDL, higher serum triglycerides and fasting insulin levels, and higher upper body obesity (measured by skin fold thickness).

Mainly in patients with pulmonary disease, airflow limitation, emphysematous changes, and pulmonary vascular abnormalities have been related to endothelial dysfunction (assessed by flow-mediated brachial artery dilation), aortic calcification, carotid intima-media thickness and arterial stiffness (Barr *et al.*, 2007; Iwamoto *et al.*, 2009; Matsuoka *et al.*, 2011). In addition, systemic inflammation (CRP, IL-6, TNF-α) has been linked to the impairments in pulmonary function as well as the atherosclerotic and hypertensive injuries in the systemic and pulmonary arteries (Poulain *et al.*, 2008; Shore, 2008; Chaouat *et al.*, 2009). On this account, endothelium-dependent and endothelium-independent vasomotor function can be involved in the individuals with the impaired lung function. Hence, vascular smooth

muscle and extracellular matrix may also be damaged, affecting the stiffness and blood flow in conduit and resistant arteries (Maclay *et al.*, 2009).

Dysregulation of lipid and glucose homeostasis, insulin resistance, neurohormonal aberrations and other abnormalities as well as coexisting local and systemic inflammation, aging, and exposure to toxic substances may all contribute to the pulmonary and vascular dysfunction.

Although plausible, some of these pathophysiological events do not apply to the young and middle-aged healthy population who constituted the main group of SPs in the current research.

Another plausible explanation that pertains to the healthy adult population with no history of cardiorespiratory disorders similar to the present research, is the parallel changes in the structural and functional properties of the airways and vessels arising from metabolic imbalance, developmental derangements, aging, and inflammatory processes.

Airway elasticity, chest wall compliance and respiratory muscle performance worsen over the course of life as do the compliance and resistance of central and peripheral vessels. With ageing, thoracic wall undergoes anatomical and mechanical modifications because of the calcification of the rib cage structures that restricts chest wall expansion and the osteoporotic fractures that change the geometry and reduce the internal space of the thorax. This also alters diaphragmatic attachments and its expansile properties, impairing respiratory muscle strength. Respiratory muscle weakness is aggravated by the age-related loss of lean (and skeletal muscle) mass and the strength of peripheral muscles due to the malnourishment and neuromuscular alterations in the skeletal muscle tissue. There are degenerative changes in lung parenchyma as well. Destruction of the elastic fibres surrounding terminal airways results in the dilatation of the alveolar ducts and homogenous enlargement of the airspaces together with a reduction in the surface area, predisposing the small airways to collapse even when breathing at tidal volumes. Alongside, collagenous structures aggregate in the bronchoalveolar wall, narrowing the small airways (Janssens, Pache and Nicod, 1999; Milic-Emili, Torchio and D'Angelo, 2007). The functional consequences of these changes include reduced elastic recoil and chest wall compliance, hyperinflation, diminished expiratory flow,

increased FRC and RV, and ventilation/perfusion mismatch manifesting as steady decline in FEV_1 and FVC, with faster rate in men as compared to women (Brandstetter and Kazemi, 1983; Cardus *et al.*, 1997).

The stiffening of arterial vessels also occurs due to the gradual loss of elastic materials and laminae, accumulation of collagen fibres and glycosaminoglycans, and misalignment of the structural units of vascular connective tissue. Persistent cyclic stress placed over the elastic fibres results in their rupture followed by the stretching and remodelling of the vessel wall, transferring the stress to the less extensible collagen fibres. These changes increase the pulse wave velocity generated by the earlier wave reflections from the peripheral arteries and the characteristic impedance in the ascending aorta, imposing an enormous load on the contracting LV and predisposing to LV hypertrophy and dysfunction (O'rourke, 1990; Debelle and Tamburro, 1999).

Importantly, the present research found significantly independent association between increase in MAP, as a good indicator of arterial stiffness and reduced elasticity, and the decline in all three spirometric parameters. This implies that there should be a link between diminished compliance and elastic recoil in thorax, manifested as the reduction in vital capacity (FVC), expiratory flow rate (FEV_1) and small airway diameter ($FEF_{25-75\%}$) and declined elasticity of large arteries and perhaps increased resistance of medium-sized or small peripheral arteries. In addition, this relationship is moderated in part by whole-body metabolic status (indicated by FM/FFM ratio). In this piece of research, the negative influence of elevated MAP on lung function was ameliorated in SPs with proportionally lower FFM.

Arterial stiffness has been found in adults with emphysema (McAllister *et al.*, 2007). Moreover, these individuals have higher expression of anti-elastin antibodies (Lee *et al.*, 2007). CRP and IL-6 are independent contributors to the spirometric and radiographic changes in lungs as well as the markers of reduced vascular elasticity even in otherwise healthy individuals (Yasmin *et al.*, 2004; Sabit *et al.*, 2007; Faner *et al.*, 2014). The role of subclinical autonomic dysfunction in the narrowing of the airways, hyperactivity of bronchial and vascular smooth muscles, and baseline vascular tone cannot be overlooked too (Engström *et al.*, 2009).

Thus, in addition to the moderating or mediating effects of body composition phenotypes, the potential role of early life experiences and inflammatory reactions appear to be more relevant to the relationships found in this study and will be discussed more extensively in the next chapter.

This study added new lines of evidence to the possible connection between respiratory and cardiovascular systems and elucidated that metabolic homeostasis may modify this link via mechanisms that might involve the biomechanical determinants of vascular and airway elasticity or compliance. Also, it revealed the opposite interaction effect of metabolic balance and haemodynamic status on respiratory capacity using robust moderation analysis. To clarify these associations, better markers of lung and arterial elasticity (*e.g.*, tonometrically measured pulse wave velocity or the systemic and intrapulmonary levels of matrix metalloproteinases and elastase were not used. In addition, the effect of segmental metabolic balance on the relationship between systemic BP and spirometric parameters was not explored. The inclusion of metabolic biomarkers and more DXA-determined measures of body composition would have improved on the accuracy of the results too.

As stressed in chapter 3, the recording of blood pressure and pulmonary function were undertaken by validated instruments (COSMED Quark PFT system and OMRON automated oscillometric blood pressure monitoring device) in accordance with the protocols respectively recommended by the ATS/ERS and AHA. The accuracy of the OMRON oscillometric device has been shown to satisfy the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instrumentation (AAMI) SP10 validation criteria for both systolic and diastolic pressures (Coleman *et al.*, 2008) in the clinical setting. However, it has not been validated for research. Spirometric testing was performed using a valid modular diagnostic cardiopulmonary unit consisted of a turbine flowmeter which have been shown to meet the ATS for accuracy and precision in measuring FVC, FEV_1, $FEF_{25-75\%}$ (Ors *et al.*, 2013). It is noteworthy that, despite satisfactory precision and good level of agreement of spirometric measurements by COSMED Quark system, its upper limit of bias for FEV_1 and FVC goes (±0.5% or 0.050 L) beyond the acceptable accuracy range recommended by the ATS/ERS.As the turbine flowmeters are flow and volume-sensitive and may underestimate and overestimate

PEF and FEV_1 at low versus high tidal volumes (Jones and Mullee, 1995). The use of a pneumotachograph instead of a turbine flowmeter would have improved the accuracy of spirometric measurements. The other limitations of the study have been addressed in previous chapters.

Chapter 9

Lung Function and Systemic Blood Pressure

The role of spirometric parameters in the prediction of systemic blood pressure was explored in the OLS regression models adjusted for age, sex, ethnicity, height, AC, NC, CC, TC, FFMI, FMI, and VFA. FEV_1, FVC and FEF_{25-75} were included separately as main predictors while DBP and SBP were defined as the outcome variable.

To create standardised coefficients of determination, Z-scores of the explanatory and outcome variables were calculated. Then, Z-score were included in the regression models instead of the absolute values.

Thereafter, the interaction effect of each spirometric index and VFA on DBP and SBP was probed using moderation analysis. The moderating influence of three levels (16^{th}, 50^{th} and 84^{th} percentile) of VFA on the association between spirometric predictors and systemic BP was visualised by drawing interaction plots.

Results

9.1. Lung function as a predictor of systemic blood pressure

Models with FEV_1, FVC and $FEF_{25-75\%}$ as the spirometric predictor, could significantly explain the variations in DBP (R^2=.55, .54, .51; p<0.001) and SBP (R^2=.41, .40, and .41; p<0.001), respectively.

FEV_1 and FVC were found to be significant independent negative predictors of DBP (standardised β=-.35 and -.40, p<0.001) and SBP (standardised β=-.38, -.30, p<0.001). FFMI (standardised β=-.46 and -.54, p<0.001), female sex (standardised β=-.42, -.66, p<0.05)., and white ethnicity (standardised β=-.32, and -.44; p<0.05 and <0.001, respectively) were other significantly negative predictors of DBP in corresponding regression models while VFA (standardised β=.34 and .37, p<0.001), NC (standardised β=.29 and .28, p<0.05), TC (standardised β=.24 and .21, p<0.001),

and height (standardised β=.15 and .18, p<0.05) were identified as positive predictors. For SBP, VFA (standardised β=.42 and .45, p<0.001), height (standardised β=.23 and .17, p<0.05) and TC (standardised β=.15 and .13, p<0.05) were significantly positive covariates whilst female gender remained a negative predictor (standardised β=-.60 and -.58, p<0.001) in the models incorporating FEV_1 and FVC, respectively. $FEF_{25-75\%}$ also contributed significantly to the prediction of DBP (standardised β=-.16, p<0.001) and SBP (standardised β=-.22, p<0.001). Age, ethnicity, NC, CC, TC, FFMI and VFA were the significant covariates of DBP whereas sex, VFA and TC remained significant predictors of SBP in these models.

Taken together, FEV_1 was the strongest spirometric predictor of DBP and SBP, with about 0.5 and 0.4SD (equal to 5.5mmHg and 5mmHg) decrease in DBP and SBP per 1SD (0.9L) increase in FEV_1.

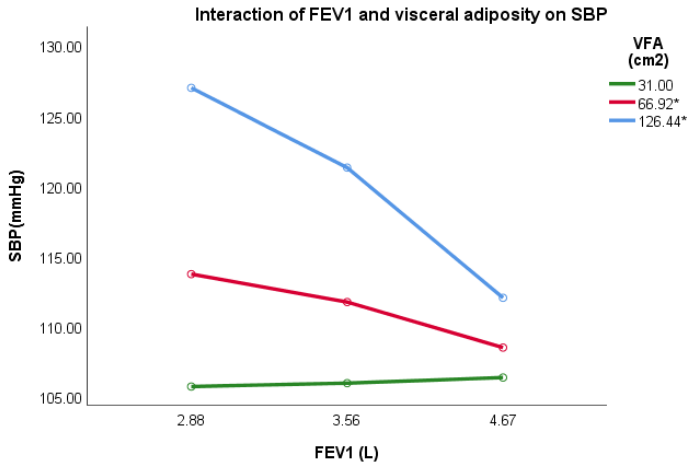
Thus, it can be inferred that lung function and blood pressure have mutual associations that are modified partially by total and/or segmental body composition phenotypes. Further, anthropometric measurements, particularly neck, calf and thigh circumferences play significant roles in the prediction of systemic blood pressure and pulmonary function, independent of total quantity of body fat or lean mass.

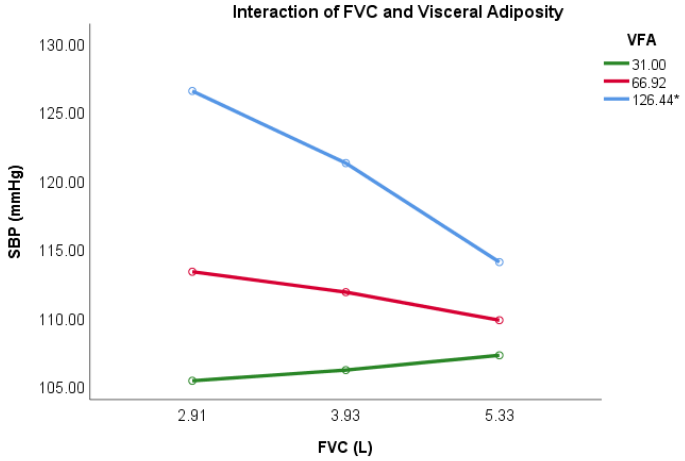
9.2. Moderation of lung function effect on systemic blood pressure by visceral adiposity

As VFA was identified as a significant covariate in the association of lung function parameters with DBP and SBP, the moderating effect of visceral adiposity on this relationship was probed in the OLS regression models adjusted for age, sex, ethnicity, height, NC, CC, TC and grip strength.

The moderation analysis revealed that the effect of all three spirometric indices on SBP was conditioned on visceral adiposity (Figure 9.1). Variations in SBP were predictable by changes in FEV_1, FVC and $FEF_{25-75\%}$ at VFA values greater than 59.2cm^2, 67.45 cm^2 and 59.68 cm^2, respectively. SBP would rise significantly by 2.9mmHg (β=-2.92; 95%CI (-5.08, -.776), p<0.01) and 8.35mmHg (β=-8.35; 95%CI (-10.67, -6.03), p<0.001) per 1L decrement in FEV_1 at middle (50^{th} percentile) and high (84^{th} percentile) levels of VFA. Each 1L decrease in FVC was significantly

predictive of about 5mmHg rise in SBP at 84th percentile of VFA (β=-5.14; 95%CI (-6.72, -3.57), p<0.001). For each 1L/s decline in FEF $_{25-75\%}$, 1.7mmHg (β=-1.75; 95%CI (-2.87, -.635), p<0.01) and 5.6mmHg (β=-5.63; 95%CI (-7.02, -4.24), p<0.001) elevation in SBP were predictable at 50th and 84th percentiles of VFA.





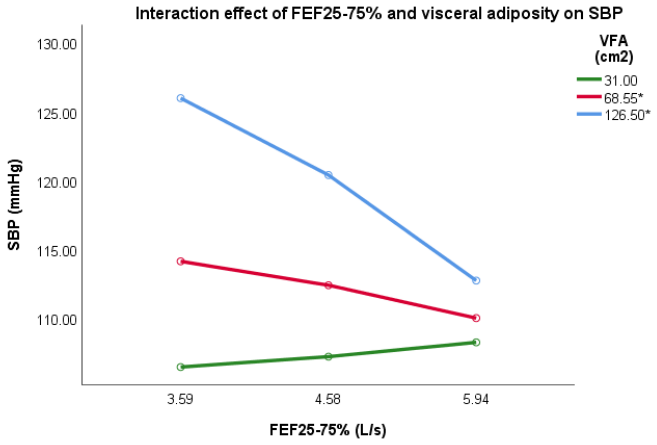


Figure 9.1. Moderating effect of visceral adiposity on SBP relationship with a) FEV_1, b) FVC and c) $FEF_{25-75\%}$.

VFA values represent 16th, 50th and 84th percentiles.

**VFA level with significant effect of spirometric parameters on SBP.*

SBP: systolic pressure; VFA: visceral fat area; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC

In contrast, visceral adiposity did not moderate the effect of spirometric indices on DBP except $FEF_{25-75\%}$. At middle and high levels of VFA, 1L/s decrease in mid-expiratory flow rate was respectively associated with about 1.7mmHg (β=-1.69; 95%CI (-2.78, -.608), $p<0.01$) and 3mmHg (β=-3.09; 95%CI (-4.38, -1.81), $p<0.001$) increase in DBP.

These observations suggest that the contribution of visceral adiposity to the inverse association between pulmonary function and haemodynamic parameters varies by the components of systemic pressure. Whilst increases in systolic pressure per decremental changes in spirometric indices occurs in otherwise healthy adults with moderate to high levels of visceral fat, the opposite changes in spirometric parameters (FEV_1, FVC) and diastolic pressure are independent of visceral adiposity.

FFMI, however, significantly moderated the effects of all three lung function measures on DBP (Figure 9.2). DBP rose by 3.3mmHg (β=-3.35; 95%CI (-5.88, -.832), $p<0.01$) and 7.3mmHg (β=-7.30; 95%CI (-8.80, -5.81), $p<0.001$) per 1L fall in FEV_1 at middle and high levels of FFMI with significant transition at FFMI >16.95kg/m^2. 1L decline in FVC was associated with about 5mmHg elevation in DBP at 84th percentile of FFMI (β=-5.13; 95%CI (-6.53, -3.72), $p<0.001$). Significant effects were observed in SPs with FFMI larger than 17.77kg/m^2. At high level of FFMI, DBP also increased by approximately 3.7mmHg (β=-3.72; 95%CI (-4.74, -2.71), $p<0.001$) per 1L/s decline in $FEF_{25-75\%}$. No significant interaction was observed between spirometric parmeters and FFMI in relation to SBP.

This is in contrast to the moderating role of visceral fatness. Here, total leanness influenced the inverse association of the dynamic lung capacity and diastolic pressure. The opposite changes in spirometric parameters and systolic pressure were, however, independent of leanness.

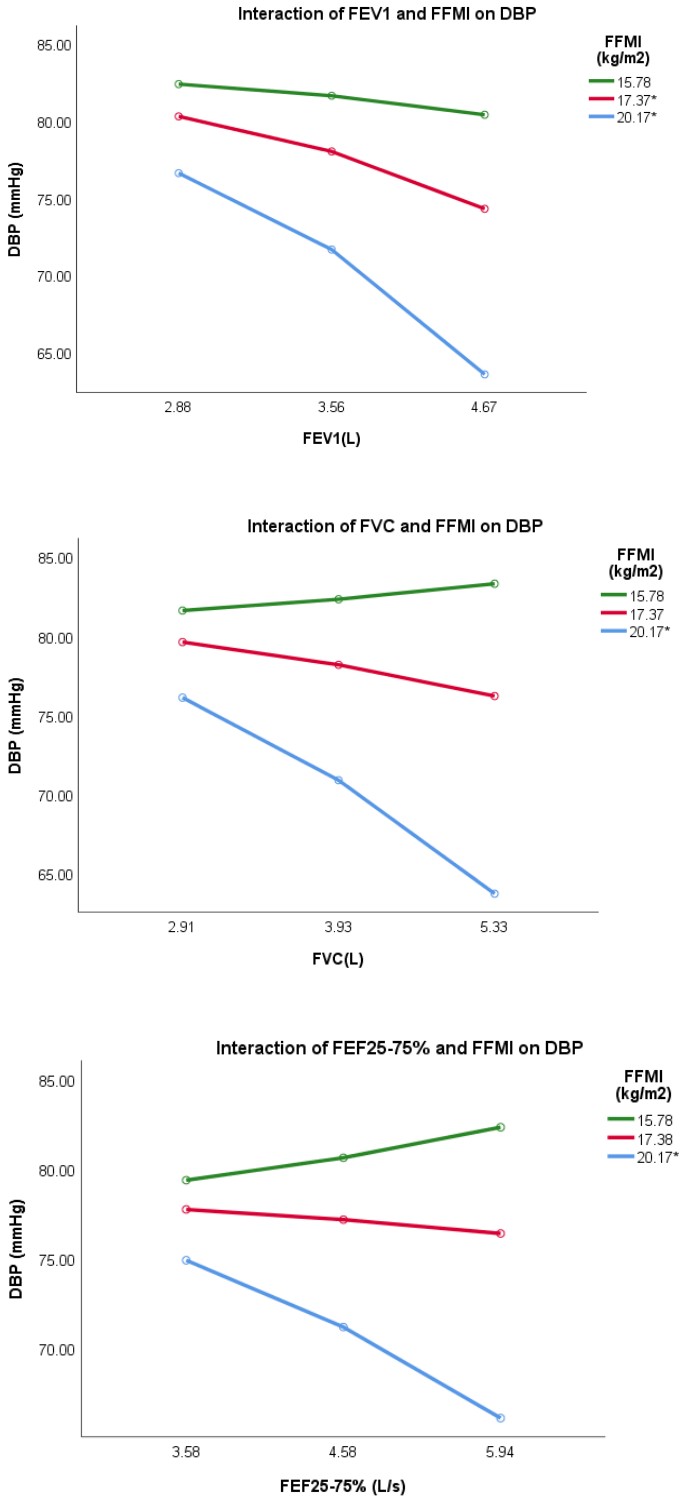


Figure 9.2. Moderating effect of FFMI on DBP relationship with a) FEV_1, b) FVC and c) $FEF_{25-75\%}$.

FFMI values represent 16th, 50th and 84th percentiles.

**FFMI level with significant effect of spirometric parameters on DBP.*

DBP: systolic pressure; VFA: visceral fat area; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC.

Discussion

In the current research, FEV_1, FVC, and $FEF_{25-75\%}$ were the independent negative predictors of diastolic and systolic pressure, adjusting for age, sex, race, anthropometric measures, as well as fat and lean mass indices. This corroborates with the previous cross-sectional and longitudinal reports on the inverse association between pulmonary function and systemic blood pressure in adults. In the normative aging study (Sparrow *et al.*, 1988), lower residual (age and height adjusted) FVC predicted higher 10-year incidence of hypertension in normotensive white men controlling for age, BMI, smoking, alcohol intake, DBP, SBP and electrocardiographic (ECG) abnormalities. In an exploratory analysis of data from the Kaiser Permanente Multiphasic Health programme, reduced FEV_1 and FVC were reported as the significant precursors of subsequent hypertension in adults, independent of their race, sex, height, BMI, smoking, alcohol consumption, salt intake, serum chemistry , baseline DBP and SBP, heart rate and chest X-ray abnormalities (Selby, Friedman and Quesenberry, 1990). A similar trend was also observed in the PRC-US Cardiopulmonary Epidemiology Study where the absolute and height-standardised FEV_1 and FVC were inversely associated with DBP and SBP in north and south Chinese women and north Chinese men cross-sectionally even after adjustment for age. Prospectively, lower initial FEV_1 and FVC were significant predictors of increased 4-year risk of developing hypertension in south Chinese women adjusting for age, BMI, smoking, socioeconomic status and baseline SBP (Wu *et al.*, 1998). These findings were further expanded by the results of the CARDIA study which disclosed a significant role of longitudinal (10 and 20 year) decline in FVC (and FEV_1) in the prediction of future hypertension (after 10 years) in black and white American adults after adjustment for age, sex, race, height, BMI, smoking, physical activity, history of asthma and SBP, indicating significant relationships between inter-and intra-individual changes in pulmonary function and the risk of elevated blood pressure (Jacobs *et al.*, 2012). Several explanations have been offered for these observations in free-living adults without pulmonary disease. One possibility is the contributory role of age as it relates to lung function and blood pressure changes oppositely. Accordingly, the strength of association between spirometric parameters and measures of systemic blood pressure diminished

appreciably in Chinese adults from the PRC-US CES cohort (Wu *et al.*, 1998). Nevertheless, (height and age adjusted) Z-scores of FVC and FEV_1 remained significantly related to SBP, DBP and the relative risk of hypertension. The confounding effect of cigarette smoking is unlikely because, in a majority of the available studies, the associations were observed in non-smokers too and the inclusion of smoking history in the predictive models did not influence the significance of associations between lung function and BP (Selby, Friedman & Quesenberry, 1990 ; Sparrow *et al.*, 1988 ; Wu *et al.*, 1998) . The role of hypoxemia is improbable as the subjects of these studies had a relatively normal vital capacity at baseline and over time. Reduced lung compliance caused by the underlying left ventricular hypertrophy and secondary interstitial pulmonary oedema is also an implausible mechanism because the relationships between spirometric indices and systemic BP and/or hypertension were independent of ECG and radiographic markers of LVH as well as baseline BP in these studies. Quantity and distribution of fat and lean mass can be more plausible explanations for the observed associations. It has been proposed that reduced lung function can be a phenotypic physiologic marker of (central) obesity and physical inactivity (Weiss, 1991), known to be significant cardiorespiratory risk factors. FEV1 and FVC have been consistently shown to be negatively related to anthropometric and body compositional measures of total and truncal adiposity across sex and age groups (Chen *et al.*, 2007; Fenger *et al.*, 2014; Santamaria *et al.*, 2011; Wannamethee, Shaper & Whincup, 2005). In the CARDIA study, proportional HR for subsequent hypertension decreased substantially after BMI adjustment although FEV_1 and FVC retained their significant effects (Jacobs *et al.*, 2012). The strength of lung function and raised BP was also greater in the American cohorts with higher prevalence of obesity as compared to Chinese adults (Wu *et al.*, 1998). Nonetheless, there has been no study exploring the interaction of direct measures of fatness and spirometric parameters on BP so far. Restricted lung and chest wall compliance reflected as reduced FVC as well as the loss of elastic recoil and increased airway resistance indicated by decreased FEV_1 may result from the abnormal accumulation and distribution of fat depots (Babb, Wyrick, *et al.*, 2008; King *et al.*, 2005; Salome, King & Berend, 2010; Sutherland *et al.*, 2008) . Moreover, pulmonary and systemic inflammatory and immunometabolic responses triggered or mediated by central adiposity may worsen lung capacity and respiratory muscle function. The interaction of visceral adiposity

and insulin resistance may also impair lung function (Cardet *et al.*, 2016; Sadeghimakki & McCarthy, 2019; Shore, 2008; Thyagarajan *et al.*, 2010). In parallel, excess adiposity, particularly of central type, precedes elevation in SBP and DBP and increases the risk of hypertension via several mechanisms, including tubuleglomerular compression (Hall *et al.*, 2014), stress-induced kidney injury (Unger *et al.*, 2013), activation of renin angiotensin aldosterone and sympathetic nervous system (Lohmeier and Iliescu, 2013), endothelial dysfunction (Hall et al., 2015) and vascular stiffening (Lyon, Law and Hsueh, 2003). In contrast, total and regional, particularly trunk and lower limb muscle mass, are positively associated with spirometric indices and ventilatory capacity in young and elderly populations (Enright *et al.*, 1994; Lazarus *et al.*, 1998; Karacan *et al.*, 2008; Martín Holguera *et al.*, 2017). Age, inactivity, and pathology-related loss of lean mass and muscle strength deteriorate respiratory performance and ventilatory function due to reduced elastic recoil, chest wall compliance and respiratory muscle function (Watsford, Murphy and Pine, 2007). Despite inconsistent findings, it has been suggested that total and segmental (except lower limb) muscle mass may be positively associated with elevated SBP and DBP and the risk of subsequent hypertension in different populations (Peppa *et al.*, 2014; Vaziri *et al.*, 2015; Ye, 2018). In addition, intramuscular fat infiltration in lower limbs has been shown to be an independently significant predictor of incident hypertension (Zhao et al., 2017). Moreover, an interaction effect of abdominal obesity and upper-limb leanness on the prevalence of metabolic syndrome has been found in postmenopausal women (Peppa *et al.*, 2014). LVH and carotid wall thickening, arterial stiffness (Leischik *et al.*, 2014; Moreno *et al.*, 2015), myofiber type shift in hypertrophied muscles (DiCesare *et al.*, 2017), and SNS activation(Saito, Iwase and Hachiya, 2009) have been proposed as the putative mechanisms underlying BP-raising effect of high skeletal muscle mass. This indicates that the association between pulmonary function and systemic BP can be moderated by the combined effect of fat and lean compartments of body composition.

In agreement with this hypothesis, the present study found that FFMI, VFA, and NC were significant predictors of spirometric and sphygmomanometric parameters in separate multivariable regression models. Notably, visceral adiposity and total leanness differentially affected the association between lung function and

haemodynamic status. Whereas lower $FEV_{1,}$ FVC and $FEF_{25-75\%}$ predicted increased systolic pressure in individuals with excessive visceral fatness (>60 cm^2), the inverse association of $FEV_{1,}$ and FVC with diastolic pressure was observed in individuals with expanded fat-free compartment (>17kg/m^2). Again, the conditional BP-elevating influence of FEV_1 decline outpowered that of FVC and $FEF_{25-75\%}$ decrements. Thus, central fatness and whole-body leanness may link respiratory capacity and vascular function differentially. Further, SPs with high total and appendicular fat and skeletal muscle phenotypes had significantly increased MAP (a surrogate measure of arterial narrowing and increased peripheral vascular resistance).

Apart from body composition phenotypes, other metabolic and inflammatory processes may also play important roles in the crosstalk between respiratory and vascular systems. In a large longitudinal study of initially nondiabetic Swedish adults, baseline FVC predicted percentage in men and women was inversely associated with glucose and insulin concentrations at follow up (14 years). Further, the odds of developing insulin resistance were significantly lower in male and female subjects with higher percentage of predicted FVC at baseline controlling for sex, age at screening, follow-up time, smoking, BMI, plasma glucose level at baseline, and follow-up WHR and physical activity. Importantly, subjects with low baseline FVC% who developed IR at follow-up, had significantly higher risk of cardiovascular events over 7 years after their follow-up examination even after adjustment for sex and age, smoking, cholesterol, systolic blood pressure, waist–hip ratio, physical activity, history of myocardial infarction or stroke at the follow-up examination (Engström *et al.*, 2003). Previously, a cohort study of male participant in the Malmö preventive project had reported significantly higher levels of inflammation-sensitive plasma proteins (ISPs) in the subjects at lowest quartile of FVC adjusted for age, sex, BMI, cholesterol, SBP, recent respiratory infection, diabetes, smoking, and physical inactivity. Of note, the risk of long-term (14-year) cardiac events and cardiovascular mortality was highest among subjects with low FVC whose ISPs fell into the top quartile of concentration. Moreover, ISP adjustment attenuated the relationship between FVC and relative risk of future cardiac events (Engstrom *et al.*, 2002). Based on the findings from the CARDIA study, systemic inflammation is longitudinally associated with the impaired lung function (Kalhan *et al.*, 2010). In this cohort of young adults, higher levels of plasma fibrinogen and hs -CRP at year-7 follow-up predicted greater decline in FEV_1 and

FVC 13 years later independent of cigarette smoking, body habitus, baseline lung function and demographic factors. In the Whitehall II Study (Gimeno *et al.*, 2011), baseline and 12-year changes in hs -CRP and IL-6 concentrations were independently associated with deteriorated spirometric parameters (FVC and FEV_1) among subjects without pulmonary disease.

In a separate data analysis of the CARDIA study, it was shown that subjects at the lowest quartile of intercellular adhesion molecule (ICAM)-1, a key player in the initiation of inflammatory responses in the endothelium of pulmonary and systemic arteries expressed on the surface of endothelial cells and pneumocytes, concentration quartile had significantly higher FEV_1 and FVC 5 years later (Thyagarajan *et al.*, 2009) after discounting for race, gender, height, age, physical activity, smoking status, alcohol intake, BMI, and asthma status. Interestingly, baseline (year 5) and time-dependent changes (between year 5 and 10) in FEV_1 and FVC were predictive of year-15 ICAM-1 concentration, with lower quartiles and larger decline in the spirometric parameters being associated with higher ICAM-1 concentration. Formerly, the age and BMI-independent association of plasma fibrinogen with longitudinal (5-and 10 year) decline in $FEV_1$and FVC had been reported in a substudy of the CARDIA involving healthy adults aged 22–36 (Thyagarajan *et al.*, 2006). It is noteworthy that no significant relationship was found for FEV_1/FVC in the above studies, indicating the potential contribution of low-grade inflammation to a restrictive rather than obstructive pattern of impairment or an early-stage deterioration in lung function among healthy population.

As a further evidence for the concomitant changes in the inflammatory profile and pulmonary function, the aggravation of systemic inflammation (assessed by CRP) over 8 years was significantly associated with annually progressive loss of FEV_1 among young adults in in the European Community Respiratory Health Survey (ECRHS) notwithstanding the non-significant relationships between these variables at baseline (Shaaban *et al.*, 2006). The involvement of inflammation and endothelial dysfunction in the interplay between lung tissue and the vasculature was supported by the results of the Multiethnic Study of Atherosclerosis (MESA). In this observational study of healthy adults 45 years and older, fibrinogen, hs -CRP and IL-6 demonstrated significantly negative individual associations with small artery elasticity (SAE) in men (derived from tonometric arterial waveform assessment) and

FVC in men and women adjusting for age, ethnicity, anthropometric measures, smoking, history of antihypertensive and antihyperlipdaemic medications, heart rate, and components of metabolic syndrome (Duprez *et al.*, 2013). IL-6 and hs -CRP have also been associated cross-sectionally with other tonometric parameters including augmentation index (a composite measure of central haemodynamic and peripheral oscillatory compliance) and carotid-femoral pulse wave velocity (cfPWV) in normotensive and hypertensive adults (Yasmin *et al.*, 2004; Mahmud and Feely, 2005; Schnabel *et al.*, 2008) as well as patients with COPD (Sabit *et al.*, 2007). However, this association was not confirmed in a larger cohort of COPD patients where emphysema severity determined by high resolution CT and MAP significantly predicted carotid-radial PWV measured by applanation tonometry but hs -CRP did not contribute significantly to the variations in PWV.

The putative linking mechanisms include reduced nitric oxide bioavailability, proliferation of smooth muscle cells and the accumulation of non-elastic ECM (Chadwick and Goode, 2008).

Given the fact that these inflammatory markers also increase the risk of cardiovascular disease (Ernst and Resch, 1993; Danesh *et al.*, 1998), it can be postulated that local and systematic inflammatory and metabolic reactions underpin pathophysiologically parallel processes in the structural units of respiratory and vascular organs, including bronchoalveolar epithelium, endothelium, and smooth muscle cells, leading to airway remodelling, loss of elastic recoil, small airway narrowing, endothelial dysfunction, reduced vascular elasticity and non-atherosclerotic arterial stiffness and carotid wall thickening (McAllister *et al.*, 2007; Mills *et al.*, 2008), aggravating the afterload and pulse pressure width with subsequent LVH, vascular remodelling, atheromatous plaque formation and essential hypertension (Lacolley *et al.*, 2002). The observation of the significant association of $FEF_{25-75\%}$, a measure of small airway involvement, DBP and SBP in the present study is in line with the notion that structural changes in peripheral airways and peripheral arteries may occur contemporaneously. In addition, the stronger effect of FEV_1 on DBP and SBP as compared to FVC and $FEF_{25-75\%}$ may indicate that vascular physiology (including elasticity and resistance) is more closely related to the airway resistance and lung compliance rather than lung volume and small airway patency. Although not tested in the current research, poor lung function

(reflected by decreased FEV_1) was found to be an independently significant predictor of pulse pressure widening (an indicator of reduced arterial compliance and elasticity) in a cross-sectional analysis of healthy adults older than 40 years (Jankowich, Taveira and Wu, 2009). Impaired respiratory capacity has also been significantly associated with increased aortic PWV, as a more accurate measure of central arterial stiffness. In an evaluation of otherwise healthy male cohorts from the Caerphilly Prospective Study (CaPS), FEV_1 and FVC in mid-life were inversely related to carotid-femoral PWV measurements about 20 years later even after adjustment for early life and social factors, inflammatory markers, components of the metabolic syndrome and haemodynamic features of vascular system, with FEV_1 having a larger effect size than FVC . Among the inflammatory markers, fibrinogen was the only significant predictor of long-term cfPWV (Bolton *et al.*, 2009). Of importance, spirometric parameters measured later in life did not predict PWV above and beyond the mid-life values, implying the involvement of the early life experiences in the structural and physiological attributes of cardiovascular and respiratory systems. Consistent with this speculation, growth trajectories relate oppositely to BP and lung function. In a prospective follow-up of the Northern Finland Birth Cohort (NFBC) from foetal to adult life, respiratory capacity (measured by FEV_1 and FVC) rose persistently over a continuum of birth weight and infantile weight gain in men and women independent of gestational age, maternal smoking during pregnancy, weight and height, physical activity and smoking status at 31 years (Canoy *et al.*, 2007). Also, a meta-analysis of 25000 children demonstrated that preterm birth, low birth weight and lesser infant weight gain were significant predictors of lower FEV_1 , higher FEV_1/FVC and greater risk of asthma during childhood (Herman *et al.*, 2016). Systemic BP in prepubertal period is significantly influenced by prenatal, post-natal, and early childhood growth. Findings from the Avon Longitudinal Study of Parents and Children (ALSPC) revealed that SBP at 10 years was inversely related to weight and weight for length at birth while it was directly associated with the rate of gaining weight, height and weight for height during and after infancy, with weight (total body mass) exerting the largest effect. A similar yet weaker pattern of association was also observed between DBP and the 3 size parameters at birth and during post-infancy period but not in the infancy period. Moreover, the magnitude of effect on BP was greater for post-infancy growth than for prenatal or infantile growth, especially for

DBP (Jones *et al.*, 2012). These observations are supported by the earlier finding of negative effect of birth weight and positive effect of BMI z-score changes in early school (7-11 years) and (more strongly) in late school (12-13 years) ages on adult SBP (>20 years) from the life-course path analysis of a cohort of Danish males after adjustment for their current BMI (Gamborg *et al.*, 2009). Taking the mediating role of adiposity into consideration, another follow-up of the ALSPC cohort illustrated that BMI changes from birth until later childhood (7–8.5 and 8.5–10 years) were closely related to DXA-measured fat mass in adolescence and the fact that the association between childhood BMI changes and BP at age 15 was largely attenuated by accounting for adolescent fat mass (Howe *et al.*, 2010).

Whereas the natural history of diastolic and systolic blood pressure variability track from late infancy to young adulthood, *i.e.*, individuals at the higher or lower ranks of BP maintain their positions in the cohort at any given time period (Labarthe, Eissa and Varas, 1991), it is comprehensible that haemodynamic characteristics of aorta and large conduit vessels (including elastin-collagen balance) are determined by the critical events operable during foetal and postnatal life as well as the environmental factors affecting growth in late childhood (Martyn and Greenwald, 1997).

A unifying explanation has not been presented for the aetiopathologic mechanisms linking loss of lung function and deteriorated vascular outcomes yet, but a plausible scenario can be the insidious degradation of elastic elements in the connective tissue of the alveoli and arterial wall in genetically and developmentally susceptible individuals. In patients with Marfan syndrome, a inherited connective tissue disorder caused by defective production of the extracellular matrix protein, fibrillin, which serves as a substrate for elastin, co-occurrence of aortic root stiffness and emphysema has been documented even in never-smokers (Pyeritz, 2000).

In accord with this hypothesis, increased level and activity of the elastolytic protein MMP-9 has been respectively detected in the bronchioalveolar and serum samples of emphysematous (Finlay *et al.*, 1997) and hypertensive (Zhou *et al.*, 2007) patients, especially those with LVH. Relevant to the study population of the present research, elevated levels of MMP-9 and increased serum elastase activity have been associated with arterial stiffness in healthy individuals (Yasmin *et al.*, 2006). This stiffening property is enhanced further by the pro-fibrotic action of MMP-9 which

stimulates biologically active peptides such as transforming growth factor-β (TGF-β), favouring extracellular matrix (ECM) accumulation (including increased collagen synthesis and deposition) that impairs the compliance of flexible arteries (Ahmed *et al.*, 2006).

Therefore, parallel structural and biochemical alterations in the airways and the vasculature arising from complex interplay between genetic, epigenetic and environmental factors may explain the observed associations between respiratory capacity and vascular performance in young to middle-aged healthy adults. This association could also be partially mediated via metabolic, inflammatory and neuroendocrine mechanisms that stem in part from body composition and physiologic phenotypes.

To the best of the author's knowledge, it is for the first time that the compartment-specific effect of body composition on the reciprocal changes in pulmonary function and systemic blood pressure is revealed. The statistically robust identification of body composition levels where the significantly inverse associations appear is another strength of this research. Also, the adjustment for one BP component in the models with the other component as the outcome improves the clarity of the associations. However, additional body composition compartments were not discounted in the models which incorporated a given pair of lean and fat compartment. Instead of absolute measures of body composition, total or segmental ratios could have been included as predictors to enable the exploration of metabolic homeostasis or relative body composition effect on respiratory-haemodynamic associations. Again, the interpretive yield of these analyses is limited by the lack of data on the metabolic profile, inflammatory markers, vascular stiffness, lung elasticity and airway resistance. It should also be noted that, despite established accuracy for the estimation of total and segmental lean mass and total fat mass, segmental multifrequency BIA underestimates visceral fat in adults with BMI≤35 kg/m^2 and overestimates visceral adiposity in individuals with higher BMI (Berker *et al.*, 2010).

Further research employing objective measures of haemodynamic status and elastic capacity of the respiratory and vascular system as well as markers of metabolic

overload and inflammation is required to test the hypothesis proposed by this study in a longitudinal large-scale manner.

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Chapter 10

Conclusion and Study Overview

This research provides important insights into complex relationships between body composition phenotypes, systemic blood pressure, peripheral muscle strength and pulmonary function.

It demonstrates that almost none of the conventional or non-conventional anthropometric measures are exclusively related to muscle mass in free-living healthy men and women. Although AC had strong relationships with total and segmental muscularity, only ABSI could be considered as a proxy for total and regional muscle depletion in men. In women, BMI and NBMI appeared to be the strongest anthropometric indicators of total and segmental fatness. In men, WHR, WC and WHtR were the strongest anthropometric markers of general and central adiposity whereas BMI, WHR and WC are strongest anthropometric indices of peripheral adiposity. By contrast, waist to height ratio and waist circumference could be used as the surrogate measures of adiposity in both sexes as they did not correspond to leanness indices. Nevertheless, these measures cannot differentiate optimally between central and peripheral fatness. In this regard, neck and mid-upper arm circumferences were the only anthropometric measures that specifically represented non-visceral adiposity.

High appendicular, particularly leg, fat and muscle content were respectively the only significant measures of deterioration or improvement in lung function among healthy adult males. In females, however, total and regional fat and muscle content were both inversely but non-significantly related to lung function parameters.

Further, the joint contribution of fatness and leanness to vascular function is linked markedly to diastolic and mean arterial pressures but not systolic and pulse pressures both totally and segmentally. Additionally, whole-body and segmental metabolic overload, respectively manifesting as the dominance of total and truncal fat mass over total fat-free mass and appendicular skeletal muscle mass correspond to elevated diastolic pressure more significantly than systolic pressure in healthy adults. Thus, the interaction of adipose and skeletal muscle tissue may alter

haemodynamic properties of resistance vessels to a larger extent than the elasticity and stiffness of conduit and central arteries. This finding has important clinical implications in the non-elderly population as it indicates that targeting systemic vascular resistance may be a more effective strategy for the prevention and management of high blood pressure in this group as compared to improving the compliance and distensibility of large to medium-sized vessels.

According to the present study, sexual dimorphism exists in the association of lung function with fatness leanness. In men, total and segmental adiposity had negative impact on pulmonary function while total leanness and segmental muscularity improve it. In women, however, both compartments inversely associated with lung function. Importantly, the effect of total and regional adiposity on lung volume and flow rate depends on the corresponding leanness or muscularity status. Greater overall leanness as well as truncal and appendicular muscularity may aggravate detrimental influence of excessive adiposity on the dynamic lung function in healthy adults. In a broader sense, there could be a link between metabolic homeostasis and pulmonary function. Furthermore, this relationship can be modified by systemic blood pressure and muscle strength. The dominance of metabolic load over metabolic capacity at whole-body level (FM/FFM) could worsen lung function (FEV_1 and $FEF_{25-75\%}$) if diastolic pressure is low. At segmental level (TFM/ASM), however, high systolic pressure moderates the unfavourable effect of metabolic overload on lung function (FEV_1 and $FEF_{25-75\%}$). From a physiologic perspective, this may be an indication of parallel and progressive decline in the compliance, elasticity and diameter of the airways and the vasculature. These unfavourable biological alterations may have been initiated or promoted by longstanding metabolic imbalance which first manifests segmentally as elevated systolic pressure and expiratory flow limitation and then involves the whole body and presents as diminished diastolic pressure and concomitant fall in vital capacity and flow rate.

Additionally, this research shows that the negative impact of incremental growth in whole-body and segmental metabolic burden on lung function (FEV_1, FVC and $FEF_{25-75\%}$) is exerted at higher levels of the isometric grip force. Consequently, adults with stronger hand grips may be more susceptible to the adverse effect of metabolic imbalance on respiratory capacity due to the quantitatively larger restriction of their greater baseline respiratory muscle strength.

This research also reveals a bidirectional association between systemic blood pressure and lung function. Systolic, diastolic and mean arterial pressure are independently negative predictors of spirometric parameters ($FEV_{1,}$ FVC and $FEF_{25-75\%}$). Reciprocally, FVC, $FEF_{25-75\%}$ and more strongly FEV_1, are the independent negative predictors of diastolic and systolic pressure in this population of healthy adults. Of note, total body composition phenotype (FM/FFM) modifies the influence of rising blood pressure on pulmonary function. Elevated MAP and DBP impair vital capacity and expiratory flow rate more prominently when fat-free mass exceeds fat mass. In contrast, elevated SBP predicts impaired dynamic lung function when FM predominates over FFM. Furthermore, healthy adults with larger areas of visceral fat may benefit more from the SBP-lowering effects of the increased baseline FEV_1 and FVC than those with limited visceral fat depots. In comparison, improvement in baseline FEV_1, FVC and $FEF_{25-75\%}$ would have more reducing effects on DBP in leaner adults.

Therefore, it can be postulated that the physiology of respiratory and vascular systems in healthy adults are partly linked via shared developmental and metabolic events that determine the functional properties of the airways and arteries.

Nevertheless, further research is required to elaborate on these observations. More specifically, investigating the interactive effects of body composition phenotypes, glucose and lipid metabolism, endothelial function, systemic and local inflammation, adipomyokines, matrix metalloproteinases, elastin-collagen balance and neuroendocrine factors can disentangle these complex relationships.

The present study has several strengths. This is the first study that explores the interaction effect of body composition phenotypes and blood pressure as well as muscle strength on lung function in the form of moderation analysis. For the first time, this study bases the investigation of the association between body composition and pulmonary function on the concept of metabolic load- capacity model that emphasises the importance of the balance between the physiologic potential of the organs and tissues determined during foetal life to early childhood and the metabolic burden imposed on them by the extrinsic factors during late childhood and adult life in maintaining health and well-being (Wells, 2009). Using absolute and height-adjusted total and segmental components of body composition in the current

research allows for a more comprehensive analysis and a better understanding of the crosstalk between adipose tissue, skeletal muscle and the cardiorespiratory system. It also draws an extensive correlative comparison between conventional and recently developed anthropometric measures in relation to the quantity and distribution of fat and muscle mass. Another important feature of this study is the exploration of the mutually effective link between lung function and blood pressure with the additional moderator involvement of body composition phenotypes. The inclusion of free-living non-elderly healthy adults minimises the confounding effect of pathological processes and reduces the potential interaction of other risk factors. Hereby, it forms a basis for the study of baseline relationships in the general population. From a technical perspective, employing the BODPOD system and multifrequency segmental BIA improved the precision and accuracy of estimating body composition compartments. Both techniques have demonstrated good levels of agreement with reference methods for the estimation of FFM, FM and %BF in healthy young to middle-aged men and women (Sardinha *et al.*, 1998; Fields, Goran and McCrory, 2002; Ling *et al.*, 2011; Verney *et al.*, 2015). Blood pressure measurements were undertaken using an accurate oscillometric device which has been reported to satisfy the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instrumentation (AAMI) SP10 validation criteria for both systolic and diastolic pressures (Coleman *et al.*, 2008). Spirometric testing was performed using a valid modular diagnostic cardiopulmonary unit consisted of a turbine flowmeter which have been shown to meet the ATS for accuracy and precision in measuring FVC, FEV_1, $FEF_{25-75\%}$ (Ors *et al.*, 2013). In addition, the absolute spirometric measurements were included in the analytical procedures instead of the percentage of predicted values. Adopting this approach avoids the inaccuracies arising from the inclusion of fixed percentages that ignore nonlinear relationship of FEV_1 with age and height (Stanojevic *et al.*, 2008; Miller *et al.*, 2011). Statistically, the study gains from the conditional process modelling by the PROCESS which enables the integration of moderation and/or mediation analysis in multivariable regression models and illuminates the processes by which the effect of a predictor is exerted via several modifiers on the outcome variable. This method is robust against the estimation bias and heteroscedasticity. It also facilitates probing of two and three-way interactions at different percentiles of the modifiers instead of three fixed points (-1SD, mean, 1SD). This ensures the values would not fall outside the range of the

data. The application of the Johnson-Neyman technique adds to the analytical depth of this procedure by identifying the exact values of the moderator where the significant transitions occur in the conditional effect of the predictor on the outcome (Hayes, 2012). Another statistical advantage of this research was the implementation of multiple imputations to replace the missing data. Multiple imputation is a valid method for predicting missing data based on the values of the observed data through multiple iterations (Barnes, Lindborg and Seaman Jr, 2006). Using several rounds of simulation and pooling the results of these simulations to generate a complete set of data increases the accuracy of this method. Despite the limited availability of suitable observed donor cases, PMM method performs well under small sample size ($n \leq 50$) and mild missingness($\leq 20\%$) in terms of standardised bias of mean change (the difference between the average of parameter estimates across a given number of replications and actual population parameter estimate divided by the standard error of estimate), coverage rate (the percentage of simulation replications in which the confidence interval estimates cover the actual value) and interval width (Barnes, Lindborg and Seaman, 2006).

This study has several limitations too. Relatively small sample size of the study affects the statistical power, accuracy and the outcome variance, leading to type II errors. The presence of missing data also reduces the analytical power of the study as it reduces the proportion of observed values. Even multiple imputation cannot capture the actual distribution of the missing values. The non-probability sampling method of this research introduces selection and observational bias as the study population is not representative of the general population. Although male and female sexes had relatively similar representation, white ethnicity was overrepresented. Likewise, majority of participants were younger than 50 yr. This may distort the interpretation of the results and limit the generalisability of the findings. The cross-sectional design of this research precludes the assessment of temporality and does not allow inferences about the causality of the relationships. Another shortcoming of this study is the implication of two-compartment model in the assessment of body composition. This model does not differentiate between storage and functional fat, involves the assumption of FFM constancy and does not control for interindividual variation in hydration status. Additionally, it assumes a constant ratio of mineral to protein, leading to inaccurate estimation of FM and FFM in the individuals with

compositional characteristics. Hence, the use of BIA method for the assessment of total and regional body composition in this study is still subject to estimation bias and measurement error despite adherence to calibration and measurement protocols and the employment of MF-BIA. In principle, BIA and ADP both provide estimates of body composition components based on prediction equations rather than direct measurements. Compared to DXA, MF-BIA underestimates body fat in underweight or normal-weight and fat-free mass in overweight or obese adults. On the contrary, it overestimates fatness in adults with overweight or obesity and underestimates leanness in individuals with low BMI (Shafer *et al.*, 2009). It also does not provide direct information about the subcutaneous adipose tissue and ectopic fat. In contrast, ADP overestimates body fat in underweight and underestimates it in overweight or obese subjects as compared to DXA (Ginde *et al.*, 2005). Employing DXA or imaging techniques could have been advantageous for more detailed and accurate study of body composition compartments. DXA discriminates among fat, non-osseous lean and osseous lean compartments.in can also provide estimations of visceral and subcutaneous adipose tissue. Despite its reliability and accuracy, this method is subject to intra and interlaboratory variation and may overestimate FFM depending on the model and manufacturer. The reliability of DXA is also reduced in extremes of body composition (Duren *et al.*, 2008).

Despite satisfactory precision and good level of agreement of spirometric measurements by COSMED Quark system, its upper limit of bias for FEV_1 and FVC goes (±0.5% or 0.050 L) beyond the acceptable accuracy range recommended by the ATS/ERS.As the turbine flowmeters are flow and volume-sensitive and may underestimate and overestimate PEF and FEV_1 at low versus high tidal volumes (Jones and Mullee, 1995). The use of a pneumotachograph instead of a turbine flowmeter would have improved the accuracy of spirometric measurements.

With respect to blood pressure measurement, OMRON M7 has been validated as an accurate oscillometric SBP and DBP-measuring device for professional and home-use purposes; however, it has not been validated for research.

In terms of adjustments for potential confounders, the present research did not explore the contribution of other components of lean body mass (body water, protein and mineral) to the prediction of lung function and blood pressure. Although a large

proportion of participants were educated, moderately active and non-smoker, these factors were not used as covariates in the analyses. Although, the participants did not have a diagnosed medical condition, the study did not control for diet, alcohol consumption, allergy, cardiometabolic and inflammatory biomarkers. The assessment of plasma glucose concentration, glycated haemoglobin, lipid profile, insulin sensitivity, adipocytokine and CRP level, thyroid function, serum or urinary creatinine, serum uric acid and vitamin D status would have provided a more comprehensive analysis. Finally, the effect of extreme deviations from the mean values of body composition (including, excessive visceral adiposity, morbid obesity, high muscularity, under-fatness and sarcopenia), BP (hypertension or hypotension) , grip strength (dynapenia) or spirometric measurements (obstructive, restrictive or mixed patterns of respiratory impairment) could not be studied satisfactorily because the participants were healthy and young to middle-aged.

Collectively, this research underscores the crucial role of body composition phenotyping in the evaluation of biologic relationships between body organs, particularly respiratory and vascular systems. The present findings suggest that derangements in whole-body and segmental metabolic homeostasis can have deleterious impacts on haemodynamic and respiratory characteristics of otherwise healthy adults.

Integrating total and regional measures of adiposity and muscularity as the indicators of metabolic status in the conceptual model of metabolic load-metabolic capacity may result in more informative categorisation, more accurate risk stratification, more consistent monitoring, more effective care and support, and subsequently, more personalised treatment, resulting in lower morbidity, higher survival, and better quality of life among individuals at risk or with pulmonary, cardiovascular and metabolic disorders. However, this model should be tested in large-scale studies on a diverse group of adults with specific clinical conditions to establish its implication as an effective strategy for individualising management modalities and improving outcome measures in different subpopulations.

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Appendix A: Ethical Approval

LONDON METROPOLITAN UNIVERSITY

LONDON MET RESEARCH ETHICS REVIEW FORM

For Research Students and Staff

Postgraduate research students (MPhil, PhD and Professional Doctorate): This form should be completed by all research students in full consultation with their supervisor. All research students must complete a research ethics review form before commencing the research or collecting any data and no later than six months after enrolment.

Staff: This form should be completed by the member of staff responsible for the research project (i.e. Principal Investigator and/or grant-holder) in full consultation with any co-investigators, research students and research staff before commencing the research or collecting any data.

Definition of Research
Research is to be understood as original investigation undertaken in order to gain knowledge and understanding. It includes work of direct relevance to the needs of commerce, industry, and to the public and voluntary sectors; scholarship*; the invention and generation of ideas, images, performances, artefacts including design, where these lead to new or substantially improved insights; and the use of existing knowledge in experimental development to produce new or substantially improved materials, devices, products and processes, including design and construction. It excludes routine testing and routine analysis of materials, components and processes such as for the maintenance of national standards, as distinct from the development of new analytical techniques. It also excludes the development of teaching materials that do not embody original research."

Scholarship is defined as the creation, development and maintenance of the intellectual infrastructure of subjects and disciplines, in forms such as dictionaries, scholarly editions, catalogues and contributions to major research databases."

London Met's *Research Ethics Policy and Procedures* and *Code of Good Research Practice*, along with links to research ethics online courses and guidance materials, can be found on the Research & Postgraduate Office Research Ethics webpage:
http://www.londonmet.ac.uk/research/current-students/research-ethics/

London Met's Research Framework can be found here:
http://www.londonmet.ac.uk/research/current-students/research-framework/

Researcher development sessions can be found here:
http://www.londonmet.ac.uk/research/current-students/researcher-development-programme/

This form requires the completion of the following three sections:

SECTION A: APPLICANT DETAILS
SECTION B: THE PROJECT - ETHICAL ISSUES
SECTION C: THE PROJECT - RISKS AND BENEFITS

SECTION A: APPLICANT DETAILS

A1	**Background information**
	Research project title: Lean vs fat mass compartmental distribution,and the relationship between blood pressure and pulmonary function of adults, a comparative study based on nutritional status,

	physical activity and body composition
	Date of submission for ethics approval:
	Proposed start date for project:
	Proposed end date for project:
	Ethics ID # (to be completed by RERP chair):

A2	**Applicant details, if for a research student project**
	Name: Roham Sadeghimakki
	London Met Email address: ros0524@my.londonmet.ac.uk

A3	**Principal Researcher/Lead Supervisor** Member of staff at London Metropolitan University who is responsible for the proposed research project either as Principal Investigator/grant-holder or, in the case of postgraduate research student projects, as Lead Supervisor
	Name: Professor David McCarthy
	Job title: Professor of Nutrition & Health
	London Met Email address: d.mccarthy@londonmet.ac.uk

SECTION B: THE PROJECT - ETHICAL ISSUES

B1	**The Research Proposal**
	Please attach a brief summary of the research project including: • Background/rationale • Research questions/aims/objectives • Research methodology • Review of key literature in this field & conceptual framework for study • References If you plan to recruit participants, be sure to include information how potential participants in the study will be identified, approached and recruited; how informed consent will be obtained; and what measures will be put in place to ensure confidentiality of personal data.
B2	**Research Ethics**
	Please outline any ethical issues that might arise from this study and how they are to be addressed. ***NB*** *All research projects have ethical considerations. Please complete this section as fully as possible using the following pointers for guidance. Please include any additional information that you think would be helpful.* • Does the project involve potentially deceiving participants? *Yes/No* • Will you be requiring the disclosure of confidential or private information? *Yes/No* • Is the project likely to lead to the disclosure of illegal activity or incriminating information about participants? *Yes/No* • Does the project require a Disclosure and Barring Service (DBS) check for the researcher? *Yes/No* • Is the project likely to expose participants to distress of any nature? *Yes/No* • Will participants be rewarded for their involvement? *Yes/No* • Are there any potential conflicts of interest in this project? *Yes/No* • Are there any other potential concerns? *Yes/No*

B3	**If you answered yes to any of the points above, please explain.**
B4	Does the proposed research project involve: • The analysis of existing data, artefacts or performances that are not already in the public domain (i.e. that are published, freely available or available by subscription)? *Yes/No* • The production and/or analysis of physical data (including computer code, physical entities and/or chemical materials) that might involve potential risks to humans, the researcher(s) or the University? *Yes/No* • The direct or indirect collection of new data from humans or animals? *Yes/No* • Sharing of data with other organisations? *Yes/No* • Export of data outside the EU? *Yes/No* **If you answered yes to any of the points above, please explain.** Anthropometric, body composition, nutritional, spirometric, and blood pressure data is collected using standard equipment and validated methods.
B5	Will the proposed research be conducted in any country outside the UK? No If so, are there independent research ethics regulations and procedures that either: • Do not recognise research ethics review approval from UK-based research ethics services? *Yes/No* and/or • Require more detailed applications for research ethics review than would ordinarily be conducted by the University's Research Ethics Review Panels and/or other UK-based research ethics services? *Yes/No* **If you answered yes to any of the points above, please explain.**
	Does the proposed research involve: • The collection and/or analysis of body tissues or fluids from humans or animals? *Yes/No* • The administration of any drug, food substance, placebo or invasive procedure to humans or animals? *Yes/No* • Any participants lacking capacity (as defined by the UK Mental Capacity Act 2005)? *Yes/No* • Relationships with any external statutory-, voluntary-, or commercial-sector organisation(s) that require(s) research ethics approval to be obtained from an external research ethics committee or the UK National Research Ethics Service (this includes research involving staff, clients, premises, facilities and data from the UK National Health Service (NHS), Social Care organisations and some other statutory

	public bodies within the UK)? *Yes/No* **If you answered yes to any of the points above, please contact your faculty's RERP chair for further guidance.**
B6	Does the proposed research involve: • Accessing / storing information (including information on the web) which promotes extremism or terrorism? *Yes/No* • Accessing / storing information which is security sensitive (e.g. for which a security clearance is required)? *Yes/No* **If you answered yes to any of the points above, please explain. To comply with the law, researchers seeking to use information in these categories must have appropriate protocols in place for the secure access and storage of material. For further guidance, see the Universities UK publication Oversight of Security Sensitive Research Material in UK Universities (2012).**

SECTION C: THE PROJECT - RISKS AND BENEFITS

C1	**Risk Assessment**
	Please outline: • the risks posed by this project to both researcher and research participants • the ways in which you intend to mitigate these risks • the benefits of this project to the applicant, participants and any others This project poses minimal risks to either researcher or research participants. Guidelines recommended by regulatory organisations are strictly followed to minimize any potential risk of adverse events for both researcher and research participants. Defining a comprehensive set of relations between pulmonary functions of patients suffering from excess weight and their compartmental skeletal and fat mass would help the researchers to conduct clinical studies in order to find more effective strategies for management of obesity, lung disease and possibly hypertension.

Please ensure that you have completed Sections A, B, and C and attached a Research Proposal before submitting to your Faculty Research Ethics Review Panel (RERP)

Please sign this form and submit it as an email attachment to the Chair of your faculty's Research Ethics Review Panel (RERP) and cc all of the staff and students who will be involved in the proposed research.

http://www.londonmet.ac.uk/research/current-students/research-ethics/

Research ethics approval can be granted for a maximum of 4 years or for the duration of the proposed research, whichever is shorter, on the condition that:

- The researcher must inform their faculty's Research Ethics Review Panel (RERP) of any changes to the proposed research that may alter the answers given to the questions in this form or any related research ethics applications
- The researcher must apply for an extension to their ethics approval if the research project continues beyond 4 years.

Declaration

I confirm that I have read London Met's *Research Ethics Policy and Procedures* and *Code of Good Research Practice* and have consulted relevant guidance on ethics in research.

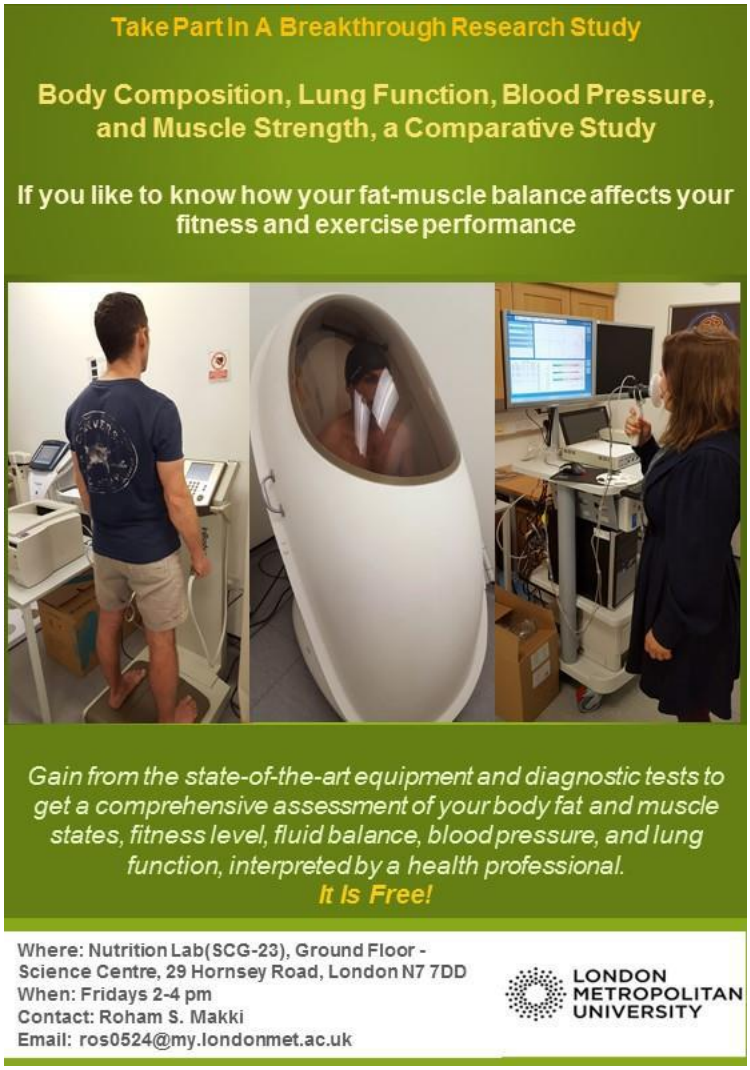
Researcher signature:...Roham Sadeghimakki.....

Date:.....23/06/2016.....

Feedback from Ethics Review Panel

	Approved	*Feedback where further work required*
Section A	Yes	
Section B	Yes	
Section C	Yes	Ethics panel discussed accompanying documentation – PIS, consent form. Additional work required. Revised documentation received 26.10.2106. Approved 26.10.2106
Date of approval		26.10.2016
NB: The Researcher should be notified of decision within <u>two</u> weeks of the submission of the application. A copy should be sent to the Research and Postgraduate Office.		
Signature of RERP chair		D. McCarthy

Appendix B: Project advertisement flyer



Appendix C: Participant Information Sheet

LONDON METROPOLITAN UNIVERSITY

PARTICIPANT INFORMATION SHEET

Full title of Project: Body composition, lung function, blood pressure, and muscle strength, a comparative study.

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

What is the purpose of the study?

Fat mass and skeletal muscle mass contribute to the alterations in lung function and blood pressure in a variety of conditions. The aim of this project will be to investigate the contribution of fat and lean mass regional distributions to respiratory function and blood pressure of otherwise healthy adults. Thereby, a solid dataset is provided which could be expanded upon further in clinical studies on respiratory, cardiovascular and metabolic diseases.

Why have I been invited to participate?

You are approached because you meet the age range and are based in the area of London where we are conducting the study. We are looking to recruit a total of 100 participants from free-living healthy adults to measure a number of parameters such as body fat mass and fat-free mass, respiratory function, blood pressure, and muscle strength.

Do I have to take part?

It is up to you to decide if you like to take part. Refusal to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason**.**

What will happen to me if I take part?

Following agreeing to take part in the study you shall be asked and assisted by a health professional to complete a health questionnaire. If you do not meet the requirements of the study at this stage, you will not be able to take part. Once you are accepted into the study, we shall assess your usual diet and will ask you to complete a physical activity and quality of life. Then, we measure your weight and height, as well as waist, hip, and thigh circumferences using a tape. Also, we shall take your blood pressure in a sitting position. Later, you will be asked to sit in a chair, take a deep breath and breathe out slowly as long as you can into a tube attached to a spirometer which assesses your lung function. It is required to repeat this manoeuvre for a minimum of three times. After a period of rest, you breathe in fully again but then blow out into the device as rapidly as you can, for a minimum of three times. Next, you will stand on the base of a body fat scale and hold the hand grips so that your body composition can be measured by sending a low, safe electrical current through the body. You will then be asked to sit very still in a large egg-shaped two-chamber unit, called BODPOD, that uses pressure changes between two chambers to determine your body density and thereby estimate your body fat percentage. Required clothing include a close-fitting swimwear and a swimming cap. Specific measures are taken into consideration for females. The BOD POD door is closed for1 minute to take the measurements, opened for 30 seconds and it is repeated one more time. While sitting inside the BODPOD, you can see the professional through a window and hear his/her voice. In in the unlikely event that you feel uncomfortable you can press the cancel button to terminate the test and exit the BODPOD.

Lastly, you will have to squeeze a handle which records the maximum force of your grip to measure your muscle strength. All procedures are undertaken in the physiology-nutrition lab at the science centre of London Metropolitan University by trained professionals.

What are the possible disadvantages and risks of taking part?

There should be no major risks as this is a body composition and spirometric study, involving no testing of new medication. It is expected that this burden would be small. This applies to all study instruments, including BIA devices and BODPOD. To minimise inconvenience, we shall arrange the date and time of the visit to the Science Centre well in advance. None of the equipment uses electromagnetic waves, including X-rays.

What are the possible benefits of taking part?

By taking part into this study, you will contribute to the development of a composite dataset consisted of parameters related to body composition, lung function, blood pressure and nutritional status of the adult population which could be used by researchers as a reference to predict and possibly improve the clinical outcomes of the patients affected by a wide range of chronic diseases. In the meantime, you will have a comprehensive check of your specified measures.

Will my data be kept confidential?

All information collected about you will be kept strictly confidential (subject to legal limitations). Access to the data will only be by researchers working on this study. Computer files will be password protected and all data, codes and identifying information will be kept in locked filing cabinets. The findings generated in the course of the research will be kept securely for a period of ten years after the completion of a research project.

What should I do if I want to take part?

If you would like to take part in this study, you can do so by contacting the researchers at the address, phone number or email address given at the end of this information sheet or by returning the reply slip in the pre-paid envelope.

What will be the next step if the results (*e.g.* spirometry test) are abnormal?

You will be advised by the professional to discuss the results (e.g. impaired lung function) with your GP.

What will happen to the results of the research study?

The results of this research will be published in a scientific journal. Your identity will not be recognisable from this. If you would like a copy of the published research you can contact the researchers at the address, phone number or email address given below following completion of the study.

Who is organising and funding the research?

This study is being conducted by Public Health Nutrition Research Group at London Metropolitan University. This research is not funded by any internal or external source.

Who has reviewed the study?

This research has been approved by the Research Ethics Committee.

Contact for Further Information:

Prof. H David McCarthy
Institute for Health Research & Policy
London Metropolitan University
Holloway Road
London
N7 8DB

Tel: 020-7133-2547
Email: d.mccarthy@londonmet.ac.uk

Roham Sadeghimakki
PhD Researcher
Public Health Nutrition Research Group
London Metropolitan University
Holloway Road
London
N7 8DB
Email: ros0524@my.londonmet.ac.uk

✂……..

PARTICIPANT NAME

PARTICIPANT ADDRESS

Please tick the box which applies:

- ☐ Yes I am interested in participating in this research. Please contact me on Home number…….Mobile number:…….

- ☐ No I am not interested in this research

Please return this slip in the stamped addressed envelope provided

Appendix D: Consent Form

LONDON METROPOLITAN UNIVERSITY

Title of Project:

Body composition, lung function, blood pressure, and muscle strength, a comparative study

FULL CONSENT FORM FOR ALL ACTIVITIES

Name of individual (capitals)_____

Please initial each statement to show your agreement

1. I confirm I have read the participant information sheet on the above project and have been given a copy to keep. I have had the opportunity to ask questions about the project and I am satisfied with the information that I have been given.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I agree to undergo the required tests and measurements in the above project. I understand that all data will be made anonymous prior to being circulated to other scientists.

4. I agree that the information gathered about me can be kept anonymously for use in future projects. I understand that researchers other than this research team may carry out some of these projects, that the results of these investigations are unlikely to have any implications for me personally and that I will not receive the results of my personal tests.

5. I agree to take part in the study and know how to contact the research team if I need to.

Volunteer's signature _____ Date _____

I confirm that I have fully explained the nature of this study to the abovenamed volunteer.

Co-ordinator's signature _____ Date_____