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Faculty of Environmental and Life Sciences

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Recording and Analysis of Breathing Patterns: A Physiological Marker in Asthma Management

by

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Thesis for the degree of Doctor of Philosophy

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Abstract

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This thesis explores the potential use of breathing patterns as a physiological marker in asthma management. The goal of asthma management is to achieve optimal asthma control, whose assessment currently involves the use of a combination of patient-related outcomes and established physiological markers. These asthma-related outcomes are also used to guide asthma treatment. To reduce patient burden and increase patient adherence, there is a need for supplemental markers that are minimally intrusive, do not rely on patients' perception and, preferably, can be made outside specialist clinical centres. One such marker could be the breathing patterns, but little is known about their current role in asthma management. This research primarily aimed to explore the use of specific quantifiable breathing pattern components to predict asthma control, as well as their ability to respond to a physiotherapy breathing retraining programme. To meet these aims, three studies were conducted: a) an initial equipment validation study in healthy adults (n=50) to test the criterion-validity of Structured Light Plethysmography (SLP) prior to selecting a method for breathing pattern measurements in this research; b) a correlational study involving asthma patients (n=122) to establish if absolute measurements and/or within-individual variability of the examined breathing components could primarily predict asthma control and secondary be associated with other asthma-related outcomes used in asthma management; and c) a small responsiveness study involving asthma patients (n=6) to explore if breathing pattern components were affected by a physiotherapy breathing retraining programme. This research found that SLP is a valid and responsive technology to record breathing patterns in the sitting position, during resting breathing and immediately after exercise as compared to Respiratory Inductive Plethysmography. The within-individual variability of the breathing components predicted asthma control, although their absolute measurements did not. Same results were found for the prediction of other asthma-related outcomes, such as the presence of dysfunctional breathing. No firm conclusions could be drawn regarding their responsiveness to breathing retraining, but some consistent changes in the within-individual variability of breathing components were observed. Based on all findings, this research found that breathing pattern variability can be used as a supplemental physiological marker in asthma management.

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Research Thesis: Declaration of Authorship

Print name:	Panagiotis Sakkatos
Title of thesis:	Recording and analysis of breathing patterns: a physiological marker in asthma management

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. None of this work has been published before submission

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Acknowledgements

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Abbreviations and Definitions

AB	Abdominal
AB_{amp}	Abdominal amplitude
AB_{ampexp}	Abdominal amplitude during the expiration phase
$AB_{ampinsp}$	Abdominal amplitude during the inspiration phase
AB_{ampRIP}	Abdominal amplitude measured by the Respiratory Inductive Plethysmography
AB_{ampSLP}	Abdominal amplitude measured by the Structured Light Plethysmography
ACQ_{7item}	Asthma Control Questionnaire
ACT	Asthma Control Test
AHR	Airway Hyperresponsiveness
AUC	Area Under the Curve
BMI	Body Mass Index
CO_2	Carbon Dioxide
CoV	Coefficient of Variation
$CoV_{RCampexp/ABampexp}$	Coefficient of Variation for the proportionality of ribcage amplitude to abdominal amplitude during the expiration phase
$CoV_{RCampinsp/ABampinsp}$	Coefficient of Variation for the proportionality of ribcage amplitude to abdominal amplitude during the inspiration phase
CoV_{RR}	Coefficient of Variation for the respiratory rate
$CoV_{Ti/Te}$	Coefficient of Variation for the proportionality of inspiration phase to expiratory phase
DB	Dysfunctional Breathing
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity

Abbreviations and Definitions

GINA	Global Initiative for Asthma Guidelines
ICS	Inhaled Corticosteroids
LABA	Long acting $beta_2$ agonists
M	Median value
Mini-AQLQ	Mini Asthma Quality of Life Questionnaire
NQ	Nijmegen Questionnaire
OEP	Optoelectronic Plethysmography
PEF	Peak Expiratory Flow
PNT	Pneumotachograph
QDC	Qualitative Diagnostic Calibration Method
RC	Ribcage
RC_{amp}	Ribcage amplitude
RC_{amp}/AB_{amp}	Proportionality of ribcage amplitude to abdominal amplitude
RC_{ampexp}	Ribcage amplitude during the expiration phase
RC_{ampexp}/AB_{ampexp}	Proportionality of ribcage amplitude to abdominal amplitude during the expiration phase
$RC_{ampinsp}$	Ribcage amplitude during the inspiration phase
$RC_{ampinsp}/AB_{ampinsp}$	Proportionality of ribcage amplitude to abdominal amplitude during the inspiration phase
RC_{ampRIP}	Ribcage amplitude as measured by the Respiratory Inductive Plethysmography
RC_{ampSLP}	Ribcage amplitude as measured by the Structured Light Plethysmography
ROC	Receiver Operating Characteristic Curve
RR	Respiratory Rate
SABA	Short acting $beta_2$ agonists
SD	Standard deviation
SLP	Structured Light Plethysmography

Te	Expiration time
TAA	Thoracoabdominal asynchrony
THA	Thoracoabdominal area
Ti	Inspiration time
Ti/Te	Proportionality of inspiration phase to expiration phase
Ttot	Total breathing cycle duration
Vt	Tidal Volume
95%LOA	95% of Limits of Agreement
95%CI	95% Confidence Intervals
μ	Mean value

Chapter 1 Introduction to the research topic

In this chapter, a brief outline of the contextual framework underlying this research is provided, including a justification for examining the use of specific quantifiable breathing pattern components as a physiological marker in asthma management. A summary of the thesis structure is also provided at the end of this chapter.

1.1 Recording and analysing breathing patterns: Their clinical use in asthma management

The main function of the respiratory system is to supply the body with adequate oxygen to meet the body's energy production requirements while maintaining acid-base balance by removing carbon dioxide (CO_2) (Petersson and Glenny 2014). This is established by the exchange of oxygen and CO_2 in the lungs through the movement of the air into and out of the lungs. This process is named *breathing* (known also as *ventilation* or *respiration*). Breathing can be under both voluntary and involuntary control, governed by the sympathetic or parasympathetic system respectively (Homma and Masaoka 2008).

Resting healthy breathing is commonly characterised as a rhythmic process comprising an active inspiratory phase (the time needed for inhalation-Ti) followed by a passive expiratory phase (the time needed for exhalation-Te), at a relatively constant breath frequency (known as respiratory rate-RR) and a volume of air (known as tidal volume-Vt) (Cluzel et al. 2000). This is achieved by compartmental movements of the thoracoabdominal area (THA) via the contraction of the inspiratory and expiratory muscles during the respiratory phases (De Troyer and Boriek 2011). All these breathing components contribute to the synthesis of the individuals' breathing patterns, which have been documented to remain relatively stable and reproducible over time (Shea et al. 1987; Yang 1992; Benchetrit 2000). Any change in a breathing pattern or its regularity has been reported to reflect alterations in the respiratory system (Wysocki et al. 2006). Breathing pattern stability may therefore have gained attention to be used as a sign of stability of the medical condition of patients with respiratory diseases, such as asthma.

Asthma is one of the most common worldwide chronic obstructive respiratory diseases (GINA 2018). It is characterised by variable recurring respiratory symptoms and reversible airflow limitation over time, imposing a substantial burden on patients' quality of life (Ivanova et al. 2012). Asthma is a heterogeneous condition associated with different phenotypes and pathophysiological mechanisms, such as airway inflammation, fixed airway obstruction and

hyperresponsiveness. There is no cure for asthma, even though the symptoms can be managed, using both pharmacological and non-pharmacological interventions (Bostantzoglou et al. 2015, Bruton et al. 2018). Patients with asthma therefore require long-term management with the aim of improving asthma-related quality of life and preventing exacerbations of the disease (GINA 2018). As a consequence, it is necessary for patients to be monitored regularly throughout their lives to evaluate asthma control and maintain it after optimal asthma treatment.

Asthma control (known also as asthma symptom control) refers to the extent to which the effects of asthma are minimised through optimal medication usage (GINA 2018). Asthma that is uncontrolled (known also as "not-well controlled" asthma) is present when there are a) daytime symptoms more than twice per week, b) night waking due to nocturnal symptoms, c) rescue medication usage more than twice per week and d) any activity limitation due to asthma (GINA 2018). Over the years, several instruments have been developed to evaluate asthma control. These are both subjective and objective markers, which are used in parallel for providing a multicomponent assessment of the disease.

In clinical practice, the subjective assessment involves the use of patient-related outcomes measured by validated questionnaires and the objective assessment incudes physiological markers (Grzelewska-Rzymowska et al. 2015; Alzahrani and Becker 2016). Physiological markers have been related to pathophysiological mechanisms underlying uncontrolled asthma. These methods are also used to guide different asthma treatment plans to enable the optimal management of the disease, and avoid future exacerbations (GINA 2018). However, to date, there is no single gold-standard marker to describe asthma control and guide asthma treatment, due to asthma heterogeneity (Bostantzoglou et al. 2015). The lack of a gold standard marker may not only be due to the limitations underling each available clinical measurement, but also due to the lack of strong interrelations between physiological measurements and patient-related endpoints (Bostantzoglou et al. 2015). This can cause potential misinterpretation of asthma patients' medical condition and their mistreatment. The current physiological measurements are also largely conducted within specialist clinical centres. It would be ideal if valid and reliable physiological markers could be made outside the clinical environment and be minimally intrusive to reduce patient burden and increase their adherence to monitoring process. All these stressed the research idea of identifying such supplemental physiological markers, which could be used to improve assessments of asthma control in future clinical practice.

Simply quantifiable breathing pattern components, such as timing parameters or parameters associated with the THA movements have the potential to be such physiological markers, but there is little convincing published evidence regarding their role in asthma management. Over the

previous decades, some differences in a some of these quantifiable breathing pattern components have been reported between healthy individuals and patients with asthma (Kassabian et al. 1982; Tobin et al. 1983b; Kesten et al. 1990), and among patients with different asthma severity during induced bronchoconstriction (Lennox et al. 1985; Gorini et al. 1999; Lavorini et al. 2013). However, the association between breathing timing parameters, the THA movements and asthma control is not clear. As a result, any ability of these breathing components to be used as a physiological marker for asthma control has not been established yet. This together with a paucity of data regarding their responsiveness to asthma treatment has further contributed to a gap of knowledge regarding their actual role in asthma management.

Since changes in breathing patterns may be the result of the pathophysiological mechanisms underlying the disease, measuring them has recently gained more attention (Courtney 2009; Courtney et al. 2011; Upton et al. 2012; Raoufy et al. 2016). However, there has been still little attempt to be used as indicators of asthma progress in clinical practice. This may be because clinical assessments of breathing pattern are currently based on simple clinicians' observations, lacking accurate quantification (Tulaimat et al. 2016). Using clinicians' observational methods limits the number of breathing pattern components that can be examined in parallel. Also clinicians' observational methods can make impossible to record the natural behaviour of quantifiable components of breathing pattern over long periods, compared to using technologically advanced recording methods. Recording a range of quantifiable components of breathing patterns for long periods may provide an enhanced insight into the natural behaviour and adaptability of breathing in respiratory diseases, such as asthma.

In addition to clinicians' observations, subjective questionnaires, such as the Nijmegen questionnaire (NQ), are being currently used to characterise breathing pattern disorders that are known collectively as dysfunctional breathing (DB) in asthma (Thomas et al. 2003; Courtney et al. 2011; Jones et al. 2015; Baker and Everard 2015; Bruton et al. 2018). However, the NQ was initially developed to identify symptoms of hyperventilation, based on patients' perception (Van Dixhoorn and Duivenvoorden 1985). Although hyperventilation plays a significant role in many patients with uncontrolled asthma, there is some ambiguity surrounding the nature of the relationship between the NQ scores and altered quantifiable breathing pattern components (Van Dixhoorn and Folgering 2015). The research presented in this thesis used a relative new and commercially available optical-based method to objectively quantify breathing pattern components. This was validated in this research, to measure timing components and THA movements prior to determining the potential use of breathing patterns as a supplemental physiological marker in asthma management.

1.2 Aim of the research presented in this thesis

Several technologies, both invasive and non-invasive, have been developed to allow monitoring of breathing patterns over time (Aliverti et al. 2001; Clarenbach et al. 2005; Fiamma et al. 2007; De Boer et al. 2010). However, each recording method has its limitations, and none have been fully translated into clinical practice to facilitate the routine quantification and accurate evaluation of breathing patterns in clinical settings (Folke et al. 2003; Grossman et al. 2010; Boudarham et al. 2013). The quantification of several breathing pattern components currently involves the use of complex laboratory based equipment, and requires the use of signal processing techniques to analyse breathing pattern data. Simplifying both the recording and the analysis procedures of breathing pattern measurements may therefore facilitate their more frequent and accurate assessment not only in research but also in clinical environments, such as primary care or community settings, or outside from these settings.

An ultimate future aim would be to monitor breathing patterns from the home or community settings to be used as an early indicator of asthma progress. Before meeting this future research goal, it was first necessary to understand the role of quantifiable breathing pattern components in asthma management. The primary aim of this research presented in this thesis, therefore was to explore the use of timing parameters and THA movements as a physiological marker in asthma management. To meet this aim, observational and experimental studies, using a positivistic research approach, were performed (see Table 1-1). It was hypothesised, that timing parameters and the proportion of the compartmental THA movements could be used as a physiological marker to predict uncontrolled asthma when measured on one occasion. These breathing pattern components were also hypothesised to respond to a specific adjunctive asthma treatment, known as breathing retraining.

Before testing these hypotheses, it was first necessary to identify an appropriate instrument for breathing pattern measurements, determine the validity and the responsiveness of this tool, and then apply it for the purposes of this research. After reviewing the literature regarding current monitoring methods for breathing pattern measurements, a relatively new recording method, known as the Structured Light Plethysmography, was identified as another form of technology for breathing pattern measurements. Due to a limited body of evidence examining the SLP's performance under different breathing conditions, it was deemed interesting to conduct a validation study prior to selecting a valid recording instrument for breathing pattern measurements in this research. The SLP's validation study aimed to contribute to its criterion-validity as compared to a reference-non-invasive monitoring method, known as the Respiratory Inductive Plethysmography (RIP). The primary research question in this study was: is the SLP a

valid and responsive tool to record timing parameters and THA movements during different breathing conditions compared to the RIP?

After selecting a valid recording tool for breathing pattern measurements, a correlational study was designed to primarily explore the association between quantifiable breathing pattern components and asthma control. This involved an observational cross-sectional study design used to examine whether specific quantifiable breathing pattern components, such as timing parameters and THA motion (both absolute measurements and within-individual variability) could predict asthma control, when measured on a single occasion. The research question was: can absolute measurements and/or variability of timing parameters and a parameter associated with THA movements predict asthma control? A post-hoc analysis was further performed to look at the ability of a predictive model to differentiate between patients with well-controlled and uncontrolled asthma. A standardised validated questionnaire commonly used in clinical practice was used to measure asthma control. This was the Asthma Control Questionnaire (ACQ_{7item}). Predictions of other asthma-related outcomes commonly used in asthma management, through the examined breathing pattern components were secondary sought in the same correlational study. This was to further explore their use as a surrogate marker for other asthma-related outcomes used in asthma management.

Understanding the use of a marker as an indicator of a disease can also involve the examination of its ability to be responsive enough to measure treatment effects after therapeutic interventions (Jones and Agusti 2006). This is necessary to guide treatment plans. It was therefore deemed interesting to provide additional preliminary evidence regarding the responsiveness of the examined breathing pattern components to a specific adjunctive asthma treatment known as breathing retraining (see Table 1-1). Thus, a responsiveness study was conducted and this was a single-arm uncontrolled study with repeated measures, to provide preliminary data about changes in quantifiable breathing pattern components before and after breathing retraining. The primary research question of this study was: do absolute measurements and/or variability of timing parameters and a parameter associated with THA movements change after a face-to-face physiotherapy breathing retraining programme?

1.3 Thesis structure

Chapter 2 provides an overview of both patient-related endpoints and physiological markers that are currently associated with asthma control and be used in its monitoring process. Their use to guide asthma treatment is also discussed.

Chapter 3 provides a narrative review of the literature using a systematic search approach regarding the association between specific quantifiable breathing pattern components and asthma control. This comes in line with their ability to respond to effective adjunctive asthma treatments, such as breathing retraining interventions. Gaps of knowledge in these areas are presented in this chapter along with the rationale for conducting the correlational study and the responsiveness study.

Chapter 4 provides a narrative review of the literature using a systematic search approach to identify validated recording methods for breathing pattern measurements. This was to allow the researcher to determine a valid and responsive method for measuring breathing pattern components and use it in the subsequent studies of this research. The rationale and justification of conducting the SLP's validation study prior to the selection of a valid recording technology to be used in the subsequent studies of this research is provided in the same chapter.

Chapters 5, 6 and 7 present the methodologies, the results and the individual discussions of the validation study, the correlational study and the responsiveness study respectively.

Chapter 8 provides an overall summary and a combined discussion of the key findings of this research.

Chapter 9 outlines some suggestions for the applicability of the key findings of this research together with some suggestions for future research direction.

Finally , chapter 10 provides the conclusion of this research .

Table 1-1: Outline of the studies undertaken in this research to explore the use of quantifiable breathing pattern components as a physiological marker in asthma management

Methods	Validation study	Correlational study	Responsiveness study
Primary Aim	To test the criterion-validity of the SLP under different breathing conditions as well as its responsiveness compared to the RIP	To examine whether specific quantifiable breathing pattern components are associated with asthma control	To test the responsiveness of quantifiable breathing pattern components following a physiotherapy face-to-face breathing retraining programme
Primary research question	Is the SPL a valid and responsive monitoring method for measuring timing parameters and THA movements under different breathing conditions as compared to the RIP	Can absolute measurements and/or within-individual variability of timing parameters and THA movement predict asthma control?	Do absolute measurements and/or within-individual variability of timing parameters and THA movement change after breathing retraining
Primary Hypothesis	The SLP can provide accurate measures of these breathing pattern components at rest and immediately after submaximal exercise. It is also comparable to the RIP for identifying any change in the examined breathing pattern components after exercise	Increased RR, disproportionate respiratory phases with shorter expiration phases, a shift towards greater ribcage motion to abdominal motion and/or increased within-individual variability of these breathing pattern components predict uncontrolled asthma, as measured within a single recording session	Absolute measurements and within-individual variability of timing parameters and THA movement change after breathing retraining

Continue Table 1-1

Methods	Validation study	Correlational study	Responsiveness study
Study design	Observational cross-sectional	Observational cross-sectional	Interventional, single arm (uncontrolled), test retest repeated measures study
Participants	50 adults (aged 18 or over) who could complete a 10-mitute incremental exercise protocol	122 adult patients with a clinical diagnosis of asthma were recruited and their breathing pattern components were recorded for 5 minutes within a single recording session	6 adult patients with a clinical diagnosis of asthma who had been referred for a face-to-face physiotherapy breathing retraining programme

Chapter 2 Monitoring asthma: Current markers to describe asthma control and guide asthma treatment

In this chapter, current clinical measurements associated with asthma control and used to guide asthma treatment (both pharmacological and non-pharmacological) are reviewed. Understanding the limitations underlying both subjective patient-related outcomes and physiological markers currently used in asthma management, helped to shape the research idea of identifying new physiological markers, such as breathing patterns, to be used in asthma management.

2.1 Asthma: Definition and pathophysiology

Asthma is a chronic inflammatory obstructive disease of the airways, which can appear either in early childhood or in adulthood (GINA 2018). Current epidemiological studies have shown that 334 million people have been affected with asthma worldwide (To et al. 2012). In the UK, 4.3 million adults (one out of twelve) are being given asthma treatment per annum and the National Health System spends almost 1 billion pounds on asthma treatment and patients' health care (Wong et al. 2016).

Asthma is a heterogeneous disease, due to the presence of different phenotypes associated with several pathophysiological mechanisms, resulting in reversible airflow limitation and airway obstruction in line with variable symptoms (Wong et al. 2016). Asthma symptoms can involve recurrent episodes of wheezing, chest-tightness, shortness of breath, breathlessness and cough, either during the night or early in the morning (GINA 2018). Although these symptoms are likely to be the result of the pathophysiological mechanisms underlying asthma, symptom perception intensity and frequency can differ among patients with the same severity of asthma, or within an individual over time (McCracken et al. 2017). This makes asthma an unpredictable respiratory problem, which requires patients to be monitored using objective accurate physiological markers throughout their lives.

The exact causes of asthma have not been clearly established yet, but a combination of genetic predisposition, allergen exposure, environmental triggers (such as cold air or dust) and frequent virus chest infections over time have been highlighted to trigger airway inflammation. (Holgate 2008; Rusell and Brightling 2017). Airway inflammation is a key pathophysiological mechanism underlying asthma and involves the accumulation of inflammatory cells such as eosinophils, mast cells, T lymphocytes and neutrophils in the airway mucosa and lumen (Lambrecht and Hammad 2015). The presence of inflammatory cells is likely to cause airway hyperresponsiveness (AHR).

This appears as a reduction in airway calibre in response to a chemical or physical stimulus, such as methacholine, histamine, cold air or exercise (Rusell and Brightling 2017). Additionally, morphological alterations of the airway wall, such as structural bronchial changes (known also as airway remodelling), due to oedema and cellular infiltration, can cause airway narrowing (McCracken et al. 2017). The narrowed peripheral airways can therefore close at higher lung volumes, due to airway resistance, contributing to increased residual lung volume, expiratory flow limitation or fixed airway obstruction.

Although the three key asthma mechanisms (inflammation, airway obstruction and hyperresponsiveness) are known to be related (Holgate et al. 2009), their interrelation can be variable over time, due to asthma heterogeneity (Wenzel 2012). Asthma heterogeneity mainly refers to the presence of several asthma phenotypes with some commonly identified phenotypes being allergic (known also as atopic) asthma, non-allergic asthma (known also as non-atopic), late-onset asthma or occupational asthma (Haldar et al. 2008; Papi et al. 2017).

2.2 Asthma diagnosis

An early accurate diagnosis of asthma is required to enable an optimal treatment plan, which aims to control its clinical characteristics (Wong et al. 2016). According to the Global Initiative for Asthma Guidelines (GINA) (2018), the absolute use of a single gold-standard diagnostic test can be misleading, due to asthma heterogeneity and reversibility. Therefore, asthma diagnosis is a multifactorial process based on several clinical criteria. These criteria involve the medical and family history, a physical examination, the patients' allergic sensitivities and positive signs of either reversible airflow obstruction or AHR (GINA 2018).

In clinical practice, patients with recurrent episodes of asthma-related symptoms are referred to the clinicians (see Figure 2-1). Although the presence and frequency of asthma-related symptoms are the first identifiable clinical signs, the cornerstone of asthma diagnosis is lung function tests, which can provide a direct assessment of the airways (McCracken et al. 2017). Lung function tests are performed using Spirometry, which is a well-standardised valid and reliable method to quantify airflow and forced expiratory lung volumes (Reddel et al. 2009). Decline of lung function measurements, such as the forced expiratory volume in one second (FEV_1) over the forced vital capacity (FVC) and the peak expiratory flow (PEF) compared to their predicted values reflect airflow limitation and obstruction (McCracken et al. 2017). These can occur due to the potential distortion of luminal size of airway calibre and the elastic properties of surrounding tissues.

Evidence based-guidelines have suggested that FEV_1/FVC <70% indicates the presence of airway obstruction in asthma and the severity of airway obstruction can be determined by the amount of

decrease in $\%FEV_{1predicted}$ (GINA 2018). However, the use of lung function tests in isolation to make an asthma diagnosis can be misleading in specific groups of patients, such as the elderly (Chotirmall et al 2009). This can be because lung function can be altered in the elderly due to ageing process. Consequently, there may be acceptable normal changes in Spirometry measurements without the presence of asthma. A decline in lung function is also a common clinical characteristic of other respiratory conditions, such as chronic obstructive pulmonary disease (COPD), causing doubts regarding the definite diagnosis of asthma (Postma and Rabe 2015). Hence, the diagnostic process of asthma also involves the measurement of lung function reversibility via a bronchodilator reversibility test (see Figure 2-1). An increase in the FEV_1 of more than 12% from baseline measurement and greater than 200 ml after 10-15 minute administration of an acting $Beta_2$ Agonist (such as methacholine or histamine) has been suggested as a positive sign for asthma diagnosis (GINA 2018).

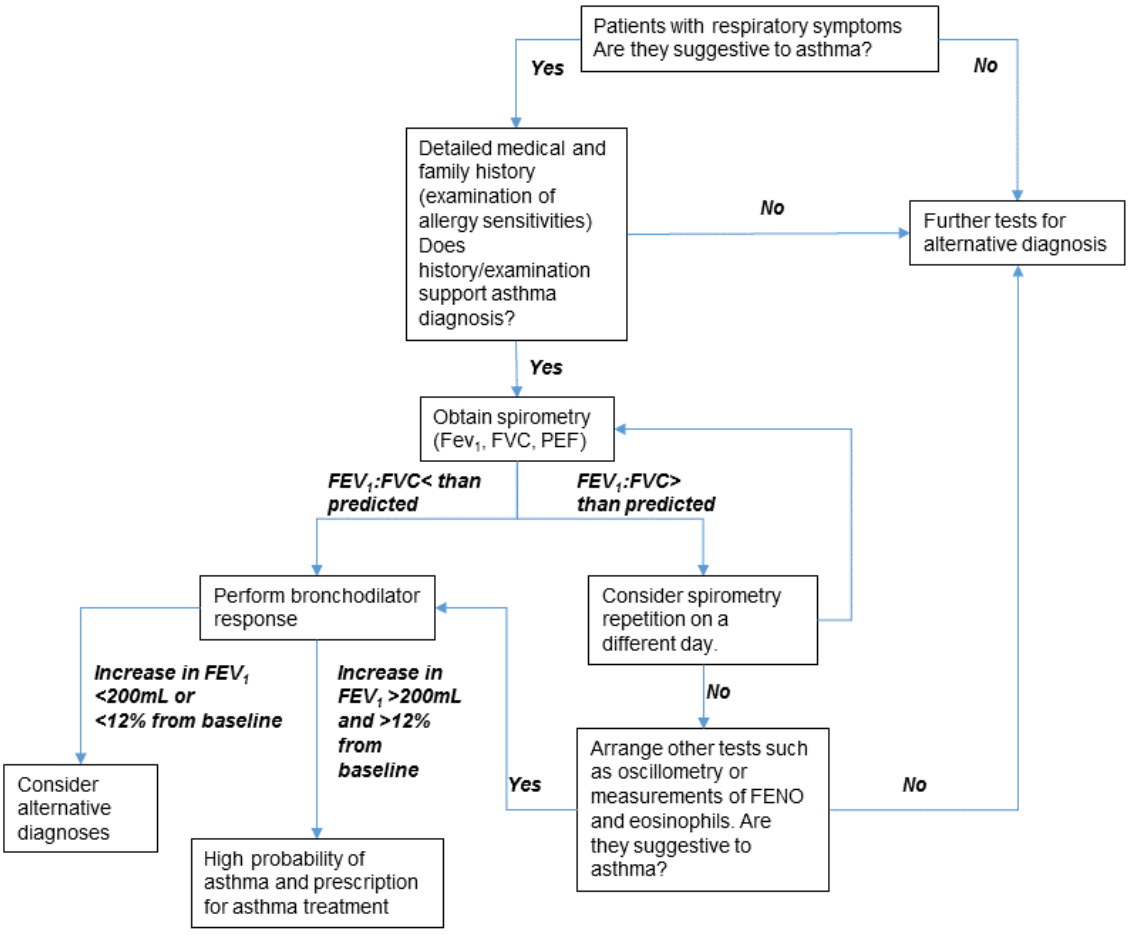


Figure 2-1: Overview of the sequence of events to make an asthma diagnosis as suggested by GINA (2018)

Although lung function tests can detect airflow limitation or fixed airway obstruction in asthma, it is not likely to reflect directly other pathophysiological asthma mechanisms. In asthma, fixed

airway obstruction can be a result of a long-term inflammation process of the airways (Holgate 2008).Therefore, the levels of inflammatory cells are monitored in parallel to aid the asthma diagnosis and confirm the presence of airway inflammation (Katz et al. 2014). The most widely documented inflammatory markers are eosinophils, identified in the sputum or the blood, and the Fractional exhaled Nitric Oxide (FeNO). This is a gaseous molecule produced by epithelial cells of bronchial wall and can be identified in exhaled breath (Van Den Toorn et al. 2001).

Impedance oscillometry is another supplemental monitoring technique, which enables the measurement of central and peripheral airway resistance for enabling asthma diagnosis without performing a forced expiration manoeuvre as required by Spirometry (Komarow et al. 2011). This may facilitate an asthma diagnosis in patients who may not be cooperative with Spirometry, such as children or the elderly. Although this valid technique does not require patients' cooperation, there is no consensus regarding its diagnostic accuracy for using it alone as a gold-standard monitoring method (GINA 2018). Other clinical signs used to aid an accurate asthma diagnosis are the presence of allergies detected via skin testing and family history, but these signs are more useful for facilitating the identification of risk factors or triggers of asthma symptoms, rather than being used as diagnostic tools.

2.3 Asthma treatment

Pharmacotherapy is the first line treatment to alleviate asthma symptoms, maintain relatively normal lung function, prevent future asthma exacerbations and improve the patients' quality of life (McCracken et al. 2017). It involves two main categories of medication, known as relievers (or rescue medication), and controllers such as Inhaled Corticosteroids (ICS) and Long-Acting $Beta_2$-Agonists (LABA) (Bostantzoglou et al. 2015). The use of relievers includes Short-Acting $Beta_2$ Agonists (SABA), which can relieve acute asthma symptoms through bronchodilation. Irrespective of the type of asthma medication, pharmacotherapy is based on an up or down stepwise approach, characterised by an increase until medication goals have been achieved, or a decrease when appropriate to minimise medication's side effects (GINA 2018).

Pharmacotherapy is tailored by asthma severity with mild manifestations of the disease requiring few and low doses of inhaled corticosteroids (ICS) compared to long-term use of higher doses of ICS from patients with severe asthma. Although a study by Haldar et al. (2008) have showed that airway inflammation, severity of asthma symptoms and the need for higher doses of medications are likely to be related, 10%-15% of patients are not likely to respond to an increase in pharmacotherapy. This may be due to a potential discordance between the type of airway inflammation (such as eosinophilic or neutrophilic inflammation) and its responsiveness to

medication resulting in high risk of side effects (Bostantzoglou et al. 2015). Therefore, current evidence-based guidelines suggest that asthma treatment should be individualised not only by the severity of the disease, but also by the phenotypic asthma clinical characteristics (GINA 2018).

The stepwise pharmacological approach suggested by GINA (2018) recommends the SABA use as needed in patients with intermittent asthma. Intermittent asthma is characterised by occurrence of symptoms less than twice a week without night awakening and with normal lung function (GINA 2018). These patients are not likely to use controllers compared to those with mild asthma. In mild asthma, regular low doses of ICS (plus as needed SABA) have been found to be effective to reduce both symptoms and asthma exacerbations (O'Byrne et al. 2001; Rodrigo 2006;Raissy et al. 2013; Bostantzoglou et al. 2015). However, it has been reported that patients with mild asthma are likely to perceive little benefit from the regular use of ICS and over-rely on the SABA use, which offers immediate relief of their symptoms (Kandane-Rathnayake et al. 2009;Williams et al. 2011).

When patients do not respond to low doses of ICS, an add-on treatment involving the use of LABA is recommended in moderate asthma (GINA 2018). However, there are controversies regarding the use of LABA alone or as an add-on therapy to low dose of ICS compared to an increase in doses of ICS without using LABA (Sindi et al 2009). Although the LABA therapy do not appear to have any anti-inflammatory effect, it appears to provide long term control of asthma symptoms permitting patients to maintain low doses of ICS and avoid potential side effects (Masoli et al 2005; Lipworth 2007). However, the chronic use of LABA has been reported to make patients resilient to their use, affecting patients' responsiveness to medication and leading to uncontrolled asthma symptoms (Salpeter et al. 2004; Kramer 2009). This may be due to a potential decrease of their broncho-protective effect, which alleviates bronchoconstriction in response to allergen exposure, exercise or any chemical stimuli such as methacholine.

When the combination of LABA/ low doses of ICS are not sufficient to control asthma symptoms, medium or high doses of ICS (plus use of LABA) can be used as a treatment plan in severe asthma (GINA 2018). Tiotropium can also be used as an alternative add-on treatment for adults with moderate to severe asthma (Patel and Shaw 2015). However, patients with severe asthma receiving high doses of ICS, are likely to experience pharyngeal and laryngeal side effects including sore throat, adrenal suppression and decrease of bone mineral density.

Irrespective of the above pharmacological treatment plans, a proportion of patients, such as 5%-10% worldwide, can remain symptomatic despite appropriate pharmacotherapy (Demoly et al. 2012). Despite the lack of responsiveness to pharmacotherapy, non-adherence to medication can be another important factor for not managing sufficiently asthma symptoms. It has been

documented that the elderly and young adults are not likely to adhere treatment plans which include regular use of ICS regardless asthma severity (Lindsay and Heaney 2013; Dima et al. 2015). Non-adherence to pharmacotherapy can be attributed to several reasons, such as poor inhaler techniques, misuse of different types of medication, patients' denial to follow treatment recommendations and poor patients' perception of severity of their clinical condition (Elliot 2006; Heaney and Horne 2012). Non-pharmacological self-management therapies to improve asthma control and quality of life have recently gained attention with up to 30% of patients reporting an interest in undertaking physiotherapeutic techniques such as breathing exercises (Ernst 2000; Slader et al. 2006).

2.3.1 Physiotherapeutic interventions: An adjunctive non-pharmaceutical asthma treatment

Although pharmacotherapy is the first line treatment plan for asthma management, persisting symptoms and poor quality of life are likely to remain suboptimal (Demoly et al. 2010). Therefore attention has been given to non-pharmacological therapies, such as physiotherapeutic interventions. However, although found to be effective in improving quality of life, there is currently no consensus regarding the actual mechanism underlying these interventions (Bruton et al. 2018).

Physiotherapeutic interventions involve breathing exercises (Bruton and Lewith 2005; Holloway and West 2007; Bruton et al. 2018), inspiratory muscle training (Lima et al. 2008; Turner et al. 2011) and physical training (Eichenberger et al. 2013) with the breathing exercises being the most commonly known intervention in research as well as in clinical practice (Bruurs et al. 2013). Breathing exercises are a multicomponent intervention including both instructional and practical phases, involving several techniques, such as the Buteyko technique, the Papworth physiotherapy, breathing retraining and yogic breathing (Bruurs et al. 2013). These have several commonalities, but also vary in the way that they are implemented. For instance, the Buteyko breathing technique encourages reduction in minute ventilation by adopting a slow breathing combined with breath holding, also known as a controlled pause (Bruton and Lewith 2005). It also involves longer expiration phases via nasal breathing. The Papworth technique additionally encourages the use of the diaphragm during slow nasal breathing to replace the use of inappropriate accessory muscles during increased respiration (Holloway and West 2007). Although the differences among breathing exercises and the examination of the exact effect offered by the different components used by each technique was beyond the scope of this research, these techniques are generally based on the same theory. This involves teaching

patients with asthma a more efficient pattern of respiration by normalising altered breathing pattern components and alleviating the hyperventilation, which can be present in patients with asthma. This is discussed in more detail in Chapter 3 (section 3.4.1).

Symptoms of hyperventilation syndrome (commonly observed in the presence of dysfunctional breathing- DB) have been found as a co-existing problem in asthma (Thomas et al. 2001). Hyperventilation is defined as the increased ventilation above metabolic requirement and is commonly reflected by an increased breath frequency, and decreased levels of CO_2. It has been considered as a secondary pathophysiological mechanism causing asthma-related symptoms (D' Angelo et al. 2001). For instance, hyperventilation has been reported to lead airways to respond by further constriction in asthma to prevent loss of CO_2, which in turn may result in bronchoconstriction and breathlessness (Lindeman et al. 1998). One of the suggested mechanisms for breathing exercises is therefore to increase levels of CO_2 by modifying breathing patterns to reduce hyperventilation.

At present, there is a convincing body of evidence suggesting breathing exercises as an effective adjunctive treatment to improve patient-related outcomes, such as quality of life (Freitas et al. 2013; Bruton et al. 2018). However, significant changes in physiological outcomes, such as CO_2 and lung function, after breathing exercises are controversial. The evidence lags behind the literature confirming the other benefits obtained by breathing exercises. The RCT by Holloway and West (2007) examined the effectiveness of the Papworth technique in asthma by comparing adult asthmatics who received this technique with those who had only a standard care. Although the intervention group was found to have better quality of life, decrease of rescue medication usage and fewer asthma symptoms than the control group, there was no significant change in levels of CO_2 between and within groups. Despite the reliance of these results on a relatively small group of mild asthmatics, systematic reviews by O' Connor et al. (2012) and Freitas et al. (2013) have further reported the above findings. These systematic reviews have concluded that breathing exercises can have an impact on patients' quality of life and can reduce asthma symptoms. However, significant increase of CO_2, decrease of airway inflammation (measured by FeNO) and improvement of lung function measurements ($\%FEV_{1predicted}$, FEV_1/FVC) could not be firmly established.

Lack of strong evidence regarding the effectiveness of breathing exercises on physiological outcomes may be attributed to methodological limitations of the current RCTs. This includes small sample sizes, different studied asthmatic populations regarding asthma severity, lack of examination of all physiological markers among RCTs, such as the levels of CO_2. Furthermore, differences in several breathing exercises as implemented in each study and the lack of adequate

information about standardised breathing exercise protocols can contribute to current contradictory results. However, a 3 group, 12-month, observer blinded, parallel group RCT by Bruton et al. (2018) has confirmed the lack of significant physiological improvements in patients with mild-to-moderate asthma. This RCT compared the use of a DVD for breathing retraining, as a digital self-guided programme for patients with asthma, with face-to-face breathing retraining sessions and with a control group receiving standard pharmacological treatment. To date, this has been the largest trial of breathing retraining in asthma reporting the effectiveness of both digital audio-visual programme of breathing retraining and face-to-face breathing retraining sessions on patients' quality of life.

Although the exact mechanism underlying breathing retraining techniques is unknown, evidence-based guidelines have recently introduced them as an adjuvant therapy for asthma management (GINA 2018). While no physiological theory underlying breathing retraining has been clearly established, it has been characterised as a behavioural intervention offering a psychological effect on patients with asthma (Thomas et al. 2017). It is well recognised that breathing retraining can reduce emotional arousal, such as anxiety (Grammatopoulou et al. 2011; Freitas et al 2013). This psychological effect may be related to the possible empowerment of the patients reducing their anxiety levels, which have been found to be related with uncontrolled asthma (Ritz et al. 2013). This may offers a better patients' perception about their symptoms, improving asthma self-management along with the improvement of their asthma-related quality of life (Bruton et al. 2018).

Regardless the suggested mechanisms underlying breathing exercises, one of the intuitively logical theories is that breathing retraining works through modifying breathing pattern components by reducing breath frequency and increasing abdominal (AB) displacement during nasal tidal breathing. To date, limited research has examined changes in a range of quantifiable breathing pattern components after breathing retraining. This is discussed in more detail in Chapter 3 (section 3.6), and stressed the need to examine the responsiveness of quantifiable breathing pattern components to a physiotherapy face-to-face breathing retraining programme as part of exploring the role of breathing patterns in asthma management.

2.4 Asthma management: Monitoring asthma control prior to applying asthma treatment

Using individualised asthma treatment plans (either pharmacological or non-pharmacological) aim to minimise asthma symptoms, maintain patients' normal lung function, preserve patients' good quality of life and avoid future exacerbations (McCracken et al. 2017). To achieve these goals,

monitoring clinical manifestations of asthma and patients' general medical condition is required throughout their life.

Global Initiative for Asthma Guidelines (1995) documented the importance of monitoring the severity of asthma to guide asthma treatment. Asthma severity is defined as the intrinsic intensity and magnitude of the clinical manifestations, which are used to tailor asthma medication (Reddel et al. 2009). After an update of the GINA in 2006, the focus changed away from monitoring the severity, and towards the importance of monitoring and achieving optimal asthma control. This was because of the chronicity and incurable clinical manifestations of this unpredictable disease, which can change over short periods irrespective of asthma severity. Asthma control (known as asthma symptom control) refers to the frequency of asthma clinical manifestations minimised by optimal asthma medication (Sorkness 2008, Taylor et al. 2008; Bostantzoglou et al. 2015).

Repeated surveys have recently shown high prevalence of uncontrolled asthma worldwide. A cross-sectional survey by Demoly et al. (2012), aimed to compare the prevalence of optimal asthma control in five European countries (including the UK) between the years 2006, 2008 and 2010. Authors stated that in the UK, there were not significant changes in the prevalence of uncontrolled asthma between 2006 (55%) and 2010 (53.5%), with uncontrolled asthma patients being hospitalised more often than those reporting controlled symptoms. The results of this survey relied on a large heterogeneous asthma population in terms of demographics and asthma severity. The epidemiological results for asthma control are consistent with findings reported by later studies, showing high incidence of uncontrolled asthma, especially in severe asthma, despite the use of appropriate treatment (Munoz-Cano et al. 2017; Lee et al. 2018). Thus, the need for frequent assessments of asthma control via validated methods has been well recognised (GINA 2018).

2.5 Subjective assessment: Validated instruments to evaluate asthma control

Approaches to evaluate asthma control and the efficacy of various therapeutic interventions in both clinical practice and asthma research, involve the methodical assessment of signs and symptoms of the disease, using well-standardised valid and responsive tools, such as questionnaires (Sorkness 2008). This method aims to provide an evaluation of the frequency of asthma-related symptoms and effects of asthma as reported by the patients over a pre-defined period, which is typically between one and four past weeks.

Table 2-1 provides an overview of the characteristics of variable questionnaires, which are used to evaluate asthma control in clinical settings or research. Questionnaires usually involve at least 4 key symptom items. These are daytime symptoms (wheezing, cough, chest tightness and dyspnoea), nocturnal symptoms (night awakenings), frequency of rescue medication usage, and patients' limitations in daily activities because of asthma (Juniper et al. 1999; Nathan et al. 2004; LeBlanc et al. 2007 Bime et al. 2012). Despite contextual similarities among the questionnaires, there are considerable differences in their scoring system, the number of included items, the recall period and the targeted patient age. There is also no consensus regarding which key symptom items have a greater impact on quantifying asthma control. As a result, composite scores allocate the same weight to all items of the questionnaires giving an overall score.

While the detailed examination of the properties of all the current questionnaires to evaluate asthma symptom control is beyond the scope of this research, the following sections provide an overview of the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT). These two questionnaires are the most widely validated tools and are currently used in both clinical practice and research (Alzahrani and Becker 2016).

2.5.1 The Asthma Control Questionnaire and the Asthma Control Test

The ACQ is a seven-item tool (ACQ_{7item}), which was specifically developed and validated to identify uncontrolled asthma as defined by the British Thoracic Society Guidelines (1990), for the management of asthma in adults (Constain et al. 1990). Juniper et al. (1999) generated a list of the most predominant asthma symptoms as reported by 100 leaders in this research field, who were also members of international asthma guidelines committees. Five out of 10 items regarding asthma symptoms, were finally included in the developmental and validation study of the ACQ_{7item} (Juniper et al. 1999). These items are: night awakening, daytime symptoms, activity limitation, shortness of breath and wheezing. The ACQ includes two additional items regarding rescue medication usage and the estimation of $\%FEV_{1predicted}$. The ACQ_{7item} is a seven-point scale, which requires patients to recall the frequency of asthma symptoms and rescue medication usage during the past week (Juniper et al. 1999; Juniper et al. 2001). The total ACQ_{7item} score is calculated as the mean of the seven items, which are equally weighted (Olaguibelet al. 2012; Cardoso et al.2014). As a result a range of scores can be obtained between 0 and 6.

The ACQ_{7item} has been validated for use as a self-administered tool in clinical settings (Juniper et al. 1999), at home or via telephone (Cloutier et al. 2012), and it has been translated in several languages (Cardoso et al. 2014).

Table 2-1: Summary of characteristics of variable questionnaires used to assess asthma control

Instrument	Age	Number of items	Recall period (weeks)	Scoring system (cut-off points)	Administration setting	Validation/reliability studies	
Asthma control questionnaire (ACQ)	>12	6	1	<0.75 well-controlled asthma 0.75-1.5 partially controlled asthma >1.5 uncontrolled asthma	Clinical setting, home, email,	Juniper et al. (1999) Juniper et al. (2000) Juniper et al. (2005)	Juniper et al. (2010) Wyrwich et al. (2011) Cloutier et al. (2012) Cardoso et al. (2014)
Asthma control test (ACT)	>12	5	4	>19 well-controlled asthma 16-19 partially controlled asthma <16 uncontrolled asthma	Clinical setting, home, phone, email, internet	Nathan et al. (2004) Schatz et al. (2006) Schatz et al. (2007) Zhou et al. (2007) Wallenstein et al. (2007)	Kwon et al. (2008) Ko et al. (2009) Kosinski et al. (2009) Sigari et al. (2011) Alpaydin et al (2012)
Asthma therapy assessment questionnaire (ATAQ)	≥18	4	4	0 well-controlled asthma 1-2 uncontrolled asthma 3-4 Very poorly controlled asthma	Clinical setting, mail, home	Vollmer et al. (1999) Vollmer et al. (2002) Chen et al. (2007)	

Continue Table 2-1

Instrument	Age	Number of items	Recall period (weeks)	Scoring system (cut-off points)	Administration setting	Validation/reliability studies
Asthma control scoring system (ACSS)	≥18	8	1	100% Totally well controlled asthma 80%-99%adequately controlled asthma 60%-79% poorly controlled asthma 40%-59% very poorly controlled asthma <40% uncontrolled asthma	Clinical setting	LeBlanc et al. (2007) Tavares et al. (2010)
Seattle asthma severity and control questionnaire (SASCQ)	>12	5	4	Not well standardised	Primary care setting	Hallstrand et al. 2009
Asthma control and communication instrument (ACCI	>17	5	1 (2 weeks for nocturnal symptoms)	Not well standardised	Clinical setting	Patino et al. 2008

Systematic reviews which revised the properties of the ACQ_{7item}, have highlighted its accuracy to quantify different levels of asthma control compared to the clinicians' ratings and other previously standardised questionnaires, such as the Asthma Quality of Life Questionnaire (AQLQ) and the mini-Asthma Quality of Life Questionnaire (mini-AQLQ) (Revicki and Weiss 2006; Alzahrani and Becker 2016). The developmental and validation study of the ACQ_{7item} by Juniper et al. (1999) suggested the ACQ_{7item} score ≤0.75 as an optimal cut-off point for showing patients with well-controlled asthma whereas an ACQ_{7item} score ≥1.5 shows uncontrolled asthma.

A recent study by Olaguibel et al. (2012) showed no strong correlation between the above suggested cut-off points and the GINA classification (2006) for asthma control. The authors found that a cut-off point of 0.5 has better diagnostic accuracy than this suggested by Juniper et al (1999), with sensitivity and specificity being 74.1% and 77.5% respectively. Furthermore, the optimal cut-off point that indicates uncontrolled asthma was found to be 1.00 with sensitivity and specificity being 73% and 88.2% respectively (Olaguibel et al. 2012). The discrepancy between these results and those suggested by Juniper et al. (1999) could be attributed to the fact that Juniper et al. (1999) used different guidelines to define asthma control compared to those used in the study by Olaguibel et al. (2012). However, to date, an ACQ_{7item} score <0.75 has been standardised to indicate well-controlled asthma with an ACQ_{7item} score ≥1.5 showing uncontrolled asthma (GINA 2018). The scores between the above optimal cut-off points indicate partially controlled asthma.

The ACQ_{7item} has also been found to have high test-retest reliability (Interclass Correlation Coefficient- ICC 0.90) in adult patients, who remained clinical stable between consecutive measurements (Juniper et al. 1999; Juniper et al. 2000). Although the ACQ_{7item} has been found to be a valid and reliable tool, concerns have been raised regarding the feasibility of collecting data of $\%FEV_{1predicted}$ in clinical settings. Therefore, several shorter versions of this questionnaire have been developed and validated over the past years. A study by Wyrwich et al. (2011) examined the comparative performance between three shortened versions of ACQ and the ACQ_{7item}. The three shortened versions of the ACQ were a five-item ACQ, including only the items related to symptoms, a six-item ACQ excluding only the item relating to the rescue medication usage and a six-item ACQ excluding the $\%FEV_{1predicted}$. All shortened versions of the ACQ_{7item}, were found to agree with the ACQ_{7item} supporting their accuracy to quantify asthma control. Also test-retest reliability of the three shortened versions of the ACQ was high with ICC scores ranging from 0.75 to 0.80 with all versions of the ACQ being highly correlated with each other (r≥ 0.97). As a result, the use of shortened versions of the ACQ_{7item} has been encouraged to be used for quantifying asthma control when the measurement of $\%FEV_{1predicted}$ can be limited. However, the use of the

ACQ_{7item} still remains the favourable option for quantifying asthma control, due to the inclusion of objective multicomponent physiological markers (Schuler et al. 2016).

In addition to the several short versions of the ACQ_{7item}, the ACT is another widely used five-item questionnaire. It was developed to facilitate the quantification of asthma control in clinical settings without requiring lung function assessments (Nathan et al. 2004). In comparison to the ACQ_{7item}, the ACT requires patients to recall their experiences regarding five items during the past four weeks. These five items were selected from a twenty-two item survey conducted by primary care clinicians and asthma specialists (Nathan et al. 2004). The items include questions regarding nocturnal symptoms, shortness of breath, rescue medication usage, the impact of asthma in daily activities and the patients' perception about their asthma control (Schatz et al. 2006). Each of the five items is assessed on a five-point Likert type rating scale, thereby giving an overall score between 5 to 25. According to the GINA (2018), an ACT score of ≥23 and a score ≤19 indicates well-controlled and uncontrolled asthma respectively.

This instrument has been validated in several languages (Vega et al. 2007; Zhou et al. 2007; Grammatopoulou et al. 2011), and in different settings including asthma specialist consultations (Nathan et al. 2004), primary care setting (Schatz et al. 2006) via email or telephone (Schatz et al. 2007). In the validation study by Schatz et al. (2006), strong association (r=0.89) was found between the ACT and the ACQ_{7item} and moderate correlation (r=0.52) was reported between the ACT and the specialists' ratings as well. High test-retest reliability of the ACT has been also found in patients with both well-controlled and uncontrolled asthma, who remained stable at baseline and follow-up visits (Nathan et al. 2004; Alvarez-Gutierrez et al. 2010). This supports its ability to give reproducible results as compared to specialists' ratings.

Despite the above, a systematic review by Jia et al. (2013) which compared the diagnostic performances of the ACT and the ACQ_{7item}, showed discrepancies among these tools for identifying uncontrolled patients with asthma, and that could be due to the different recalling periods of each questionnaire. Low correlations (r=0.17) have been also reported between the ACT and $\%FEV_{1predicted}$ (Nathan et al. 2004, Schatz et al. 2006, Alvarez-Gutierrez et al. 2010; Melosini et al. 2012). This may be, because patients with normal lung function can report variable frequency of asthma symptoms, raising questions about the actual relationship between these parameters (Ko et al.2012).

2.5.2 Responsiveness of the Asthma Control Questionnaire and the Asthma Control Test

The importance of using markers that are responsive to several asthma treatment plans has been well-recognised, as this allows clinicians to adjust asthma treatment plans (GINA 2018).

Responsiveness, known also as sensitivity to changes, is defined as the ability of an instrument to detect small changes in patients' health status that are clinically important after the implementation of effective therapeutic interventions (Cook and Beckman 2006). In asthma literature, the responsiveness of the ACQ_{7item} and the ACT has mainly been studied by examining potential changes in scores of these questionnaires and their correlations with changes in other previously well-standardised questionnaires ,such as the AQLQ, or the clinicians' ratings for asthma control after pharmacotherapy (Alzahrani and Becker 2016).

The ACQ_{7item} has been found to be responsive and detect changes in asthma control after medication therapy (Ducharme et al. 2010). The changes in the ACQ_{7item} scores have been found to be associated with those in the AQLQ or the clinicians' ratings for asthma control (Juniper et al. 1999; Juniper et al. 2005; O'Byrne et al. 2010). A difference of 0.5 points in the ACQ_{7item} has been established to be considered as a minimum clinically important difference to guide or adjust asthma treatment (Alzahrani and Becker 2016). In addition, systematic reviews, which have examined the properties of the ACT, have also supported its response to asthma treatment plans (Cloutier et al. 2012; Alzahrani and Becker 2016). Changes in the ACT have been reported to be highly correlated (r=0.81) with changes in the ACQ_{7item} even though the ACT score changes are moderately correlated with the changes of specialists' ratings for asthma control (Schatz et al. 2006). However, Schatz et al. (2009) has reported that a clinically important difference in the ACT scores is 3 points as this was associated with increased risk of future asthma exacerbations and increase in rescue medication usage.

2.5.3 Using subjective validated tools in isolation to describe asthma control

Although the use of questionnaires has been standardised to evaluate the frequency of asthma effects, this may not be an ideal method when used in isolation. These questionnaires allocate the same weight to all items providing a total composite score, even though some symptoms may have a greater impact on some patients' clinical condition than others. Beside this, evaluation of risk for future asthma exacerbations and any treatment-related side effects does not play a role in the quantification of asthma control of current questionnaires, such as the ACQ_{7item} and the ACT. These parameters have been described as some other key elements for the evaluation of asthma control (GINA 2018).

Additionally, the quantification of asthma control via the use of valid questionnaires is based on patients' recall of their experience over a specific period. Despite being subjective, the recall period, ranging from one to four weeks, has been established arbitrarily (Bime et al. 2012). Patients are required to recall their experiences based on their self-evaluation, which may not be

always an easy task for those with coexisting problems, such as emotional arousal, or complex medical conditions (Deshmukh et al. 2007; Taylor et al. 2008).

Some patients with asthma have been reported to develop catastrophic beliefs about the frequency of their symptoms, due to the unpredictable and heterogeneous nature of the disease (Thoren and Petermann 2000; Katon et al. 2004; Cordina et al. 2009). This can result in heightened emotional arousal, such as anxiety, which in turn can contribute to asthma-related symptoms such as breathlessness and chest tightness (Katon et al. 2004). As these symptoms are similar to those in asthma during a symptomatic period, they can affect patients' perception regarding the actual control of their asthma. This in turn can result in misinterpretation of their actual medical condition (Deshmukh et al. 2007; De Peuter et al. 2008).

There are some other comorbidities in asthma, such as COPD, which can mimic asthma-related symptoms. Although patients with asthma have been found to recognise asthma symptoms in response to a harmless stimulus (De Peuter et al. 2005; De Peuter et al. 2007), they are not likely to distinguish similar symptoms caused by co-existing respiratory diseases (Deshmukh et al. 2007; Yii and Koh 2013). This, in turn, can also contribute to their misconception about how controlled their symptoms are due to asthma (Henderson et al. 2007). Hence, evaluation of asthma control has been characterised as a multicomponent process, including the parallel use of objective valid and reliable physiological markers.

2.6 Physiological markers in association with asthma control

The following sections provide an overview of the most widely used physiological markers involved in the evaluation of asthma control and guidance of asthma treatment in clinical practice.

2.6.1 Lung function measurements

Monitoring lung function is an important physiological marker to assess the respiratory system in the presence of uncontrolled asthma (GINA 2018). This is performed using Spirometry and allows the identification of airway obstruction and airflow limitation (Mulholland et al. 2017). Although lung function assessment is an integral element of asthma diagnosis, there is conflicting evidence regarding the use of lung function measurements in isolation to determine asthma control.

In the observational cross-sectional study by Manoharan et al. (2015), low values of $\%FEV_{1predicted}$ were found to be associated with uncontrolled asthma when determined by the frequency of rescue medication usage and the doses of ICS. However, arbitrary cut-off points for the

medication usage were chosen to distinguish well-controlled and uncontrolled asthma, causing potential bias in the results. On the contrary, in a longitudinal observational study by Papakosta et al. (2011), the association between asthma control and $\%FEV_{1predicted}$ was examined in 160 patients before and after controller medication. Despite the lack of equal group of patients with varying asthma control both at baseline and the follow-up visit, associations between low values of $\%FEV_{1predicted}$ and low ACT scores were found only at baseline. Similar results were also reported by Grzelewska-Rzymowska et al. (2015), who reported that patients with uncontrolled asthma (ACT<19 points) had lower values of FEV_1 compared to those with well-controlled asthma (ACT>20). However, only small associations between these parameters were found, due to presence of relative normal FEV_1 values in the majority of patients (41 out of 66) with uncontrolled asthma. Thus there have been concerns about the exclusive use of such lung function measurements as a gold-standard physiological marker of asthma control.

A discrepancy between the ACT and lung function can be attributed to the patients' perception about their symptoms (Steele et al. 2012). As mentioned previously in section 2.5.3, patients may have poor perception of their symptoms irrespective of the severity of variable airflow limitation or presence of fixed airway obstruction. For instance, evidence has showed that patients with asthma can perceive persistent asthma symptoms in the presence of normal lung function measurements (Kuntz et al. 2002; Aburuz et al. 2005). The ACT does not involve the measurement of lung function to quantify asthma control, unlike the $ACQ_{7item.}$ Better associations have been reported between the $ACQ_{7\text{-}item}$ and lung function measurements (Jia et al. 2013).

The studies by Manoharan et al. (2015) and Grzelewska-Rzymowska et al. (2015) used observational cross-sectional study designs, which can have limitations, derived from measurements taken in single-time points. So strong relationships between lung function and asthma control may not have been possible to be demonstrated. The presence of uncontrolled asthma does not necessarily mean an immediate significant decline of lung function, as this is a more long-term progressive consequence of structural and functional changes in the airways due to airway remodelling (McCracken et al. 2017). Thus, assessment of variation of lung function measurements over time have been considered as a better objective physiological marker to evaluate asthma control, including also the ability to evaluate the risk of future asthma exacerbations.

Matsunaga et al. (2015) conducted a three-year longitudinal study with annual follow-ups to examine the associations between asthma control (as measured by the ACT), asthma exacerbations and lung function in 140 patients with moderate asthma. The authors reported that a decrease in FEV_1 over time can be associated well with asthma control. Patients, who had more

rapid decline in FEV_1 over the three years (-53.3 ml/year vs -13.6ml/year), had uncontrolled asthma and high risk of asthma exacerbation. An earlier study by Kitch et al. (2004) has also indicated that low FEV_1 over a period of 3 years is an independent risk factor for subsequent asthma exacerbations (as defined by the number of hospitalisations or emergency visits due to asthma worsening). Osborne et al. (2007) have supported the same findings suggesting that a $FEV_{1predicted}$<60% is a potential risk factor for asthma exacerbation despite being a risk factor for developing fixed airflow obstruction in uncontrolled asthma. Similar linear regression results have been reported by Ortega et al. (2018), which showed a relationship between the number of exacerbations and the decline of FEV_1 in severe asthma compared to previous studies involving patients with different asthma severity. The authors concluded that repeated asthma exacerbations were associated with accelerated decline of lung function resulting in fixed airway obstruction.

Fixed airflow obstruction (as defined by FEV_1/FVC <0.70) is another measure of lung function which can used in association with asthma control. A post hoc analysis of retrospective data from two double-blinded randomised twelve-week studies involving patients with mild-to-moderate asthma (n=487) and moderate-to-severe asthma (n=559) showed that patients with uncontrolled asthma were likely to appear fixed-airway obstruction compared to those with well-controlled asthma (Tashkin et al. 2014). In their study, asthma control was determined by the frequency of rescue medication usage.

In addition, bronchial airway hyperresponsiveness (AHR), has been suggested as an adjunct measure for evaluating asthma control, even though its clinical use has not clearly been established (Galera et al. 2015). The reduction in $\%FEV_{1predicted}$ is estimated after delivering doses of a provocative agent such as methacholine (Nensa et al. 2009). Recent evidence has reported that the degree of the AHR is well associated with asthma control (Brannan 2010; Grzelewska-Rzymowska et al. 2015). However, measuring the AHR is mainly used to confirm the diagnosis of asthma, rather than ongoing monitoring. This is because measuring the AHR is a time-consuming and laboratory-based technique, requiring medical supervision, which is not likely to gain patient's acceptance for frequent assessments. Thus, this technique is not currently used as a part of the routine monitoring process of asthma control in clinical settings, and is generally used primarily for research purposes.

2.6.2 Limitations underlying lung function measurements

Although current evidence supports the use of decline of lung function over time as an objective physiological marker of asthma control and asthma exacerbations, concerns can be raised for

their relationship derived from single-time measurements. Asthma symptoms are likely to be related to structural changes, occurring either in large, or small peripheral airways, due to the presence of inflammatory cells, overlaid by other factors such as patients' psychology (Carroll et al. 2002; Bai and Knight 2005). On the other hand, lung function assessment using Spirometry monitors changes in large airways (diameter >2mm) rather than small airways (Bukstein et al. 2006). This is because Spirometry measurements mainly monitor physiological elements of the respiratory system reflected by changes in the elastic recoil of the lung, the resistance of the large airways and their degree of compression after a maximal forced expiratory manoeuvre (Gonem et al. 2014). This is an effort-dependent manoeuvre at the level of total lung capacity, which also tends to exaggerate volume-dependent small airway closure. Consequently, Spirometry may not detect potential airflow limitation caused by impairment of small peripheral airways (Scichilone et al. 2009). This, in turn, may influence its actual relationship with the presence of asthma symptoms, caused by structural changes occurring in small peripheral airways.

Spirometry is an effort-dependent recording method to record lung function requiring patients' maximal cooperation. The successful performance of the forced expiratory manoeuvre has been found to be a crucial factor for obtaining valid estimations of lung function (Townsend 2011). Giner et al. (2014) explored the potential measurement errors and patient characteristics, which may contribute to failure of receiving accurate Spirometry measurements in 136 patients with obstructive respiratory problems such as asthma and COPD. The manoeuvre performed by the patients and the lack of experience were found to be some of the factors for poor accuracy of the Spirometry results. This suggests that this recording technique may be of limited value in some patients, such as very young or unco-operative individuals with cognitive impairments. These patients can be unable to follow clinicians' instructions to successfully complete lung function tests. Thus, the use of other physiological markers obtained by less effort dependent techniques could be more useful in the evaluation of asthma control.

Additionally, associations between lung function decline and asthma symptom control have been mainly studied in patients with moderate and severe asthma. It is less clear the actual relationship between lung function and asthma symptom control in mild asthma where decline of lung function may not be always present. This can cause potential discordance for the relationship between asthma control and lung function in this group of patients. Despite this, use of lung function to describe asthma symptom control may be misleading in other group of patients, such as the elderly (Yanez et al 2014). Even in the absence of asthma, there can be a linear decrease of lung function after the fourth decade of life, due to ageing process. For instance, decline in FEV_1 (25-30ml/year) after the age of 40, which is estimated in 60ml/year after the age of 65 years, has been reported (Sharma and Goodwin 2006). This can be due to the potential reduced respiratory

muscle function and the increased residual volume, due to the lack of recoil elasticity (McClaran et al. 1995; Janssens et al. 1999).

2.6.3 The Peak Expiratory Flow in association with asthma control

The Peak Expiratory Flow (PEF) is another lung function measurement that has been used as a supplemental physiological marker in asthma management. It is defined as the maximal flow of air that an individual can exhale after a full inspiration (Reddel et al. 2009). In comparison to other lung function measurements, the PEF can be obtained individually by cost-effective and small portable peak flow meters either at the patients' homes or at different clinical environments, such as hospitals or community settings (Dobra and Equi 2018). This can facilitate the self-monitoring of lung function over time. The recording of PEF variability over time has been gained attention as a supplemental physiological marker to reflect asthma progress. Although the use of the PEF to diagnose asthma is controversial, its use to describe any early deterioration of asthma control is more acceptable (GINA 2018). A decline in the PEF has been reported as an indicator of loss of clinical asthma manifestations with a PEF value <80% from its predicted being indicative of uncontrolled asthma (Myatt 2017).

A longitudinal observational study by Thamrin et al. (2011) studied, the PEF variability over time and reported that increased variability (as determined by the Coefficient of Variation - CoV%) could predict uncontrolled asthma. The PEF variability were obtained from 83 patients with moderate asthma twice per day for 4 weeks. However, in this study uncontrolled asthma was determined by mean values of patients' PEF at baseline using arbitrary cut-off points. So, the reported relationship between the PEF variability and asthma control should be interpreted with caution. Nevertheless, similar results were reported by Kaminsky et al. (2017), who examined the associations between the PEF variability over two weeks and asthma control as determined by the ACQ. Differences in the PEF measurements have been also reported among patients with severe asthma and varying asthma control both before and after medication usage, supporting its use to describe asthma control (Thamrin et al. 2011).

One of the shortcomings of this physiological marker is the violation of its accuracy by factors, such as body position of the recordings (such as standing, sitting or supine) (McCoy et al. 2010; Wallace et al. 2013). Also accuracy of the PEF measurements depend on patients' maximal effort during an expiratory manoeuvre. Monitoring the PEF requires patients to reproduce repeated similar expiratory manoeuvres with maximal effort to provide accurate values of this (Barua and O' Mahony 2005). A critical review regarding the use of portable peak flow meters in asthma has suggested that an incorrect expiratory manoeuvre can lead to significantly different PEF

measurements, which in turn can have an impact on interpretation of patients' asthma control (Self et al. 2014). Based on the dependence of lung function tests on patients' effort, there is a need for supplemental physiological markers to establish alternative methods for evaluating asthma control. Ideally, supplemental physiological markers should be obtained by minimally intrusive methods, such as non-invasive monitoring methods, which do not require maximal patients' cooperation (Self et al. 2014).

2.6.4 Responsiveness of lung function measurements to asthma treatment

The use of lung function measurements to assess their response to asthma therapy is well established in pharmacological RCTs conducted over the past years. The responsiveness of lung function measurements to variable medication plans (low doses of ICS vs high doses of ICS, continuous use of ICS vs intermittent use of ICS) in moderate and severe asthma has been reported by several authors (Kauppinen et al. 2011; Chauhan et al. 2013; Schmidt et al. 2017). However, the responsiveness of lung function measurements to non-pharmacological interventions, such as physiotherapy breathing exercises has not been established.

Changes in $\%FEV_{1predicted}$ and the PEF variability can be present either in short or long periods of time after the use of both rescue and controller medication (Huchon et al. 2009; Tepper et al. 2012). These changes have been found to be correlated with improvements in asthma symptoms and decrease of asthma exacerbations (Kauppinen et al. 2011; Schmidt et al. 2017). Double blind, double dummy RCT has shown that the $\%FEV_{1predicted}$ increases and the PEF variability decreases after administration of either low or high doses of controller medication in both moderate and severe asthma compared to placebo groups (Huchon et al. 2009). The improvements in lung function due to pharmacotherapy has mainly be attributed to an increase of airway calibre, due to the alleviation of bronchoconstriction and airway inflammation (Tepper et al. 2012). Due to the different types and doses of pharmacotherapy applied in each trial among patients with different asthma severity, there is no consensus regarding a well-standardised minimum clinically important difference in the $\%FEV_{1predicted}$ and the PEF variability. However, in general, a change of 12% in $\%FEV_{1predicted}$ and 250ml/min in the PEF have been reported to be clinically important (Huchon et al. 2009; Tepper et al. 2012).

Although lung function measurements have been reported to respond well to pharmacotherapy, the use of these markers to guide non-pharmacological therapies, such as breathing exercises, may not be adequate as mentioned previously in section 2.3.1. Lack of improvements in lung function after interventions like breathing retraining, may be due to the mechanisms underlying this type of intervention. It has been suggested that a possible physiological mechanism

underlying breathing retraining is the improvement of hypocapnia through normalising breathing pattern components, rather than changing lung function (Bruton and Thomas 2011). Consequently, the effects of this type of intervention may not be captured by assessments of lung function improvements, stressing the need to identify alternative physiological measurements, which could be used to guide this type of adjunctive non-pharmacological intervention.

2.6.5 Summary of the use of lung function as a physiological marker in asthma management

Lung function measurements (%$FEV_{1predicted}$, FEV_1/FVC and the PEF) are considered as an important objective physiological marker in asthma management (GINA 2018). However, a lack of strong associations between lung function measurements and asthma control in single-time assessments has been documented in the literature. This has raised doubts about the use of this physiological marker in isolation to describe asthma control in single time visits of patients in clinical settings. This therefore poses a need for use of composite physiological markers to achieve optimal evaluation of patients' medical condition apart from using subjective assessments based on patients' perception. The lung function measurements are also useful to guide asthma medication. However, lung function measurements are not an ideal physiological outcome for assessing treatment effects of non-pharmaceutical therapies applied in asthma management. Identification of other supplemental physiological markers may expand our current knowledge about the function of the respiratory system during symptomatic periods of asthma and may facilitate a better routine clinical assessment of the disease.

2.6.6 The use of inflammatory markers (biomarkers) in asthma management

Inflammatory markers (known also as biomarkers) have been recognised as other physiological markers for evaluating asthma control (GINA 2018). This is because they are direct measurements of ongoing inflammation within uncontrolled asthma (Snell and Newbold 2008; Wadsworth et al. 2011; Volbeda et al. 2013). In broad terms, biomarkers are objective indicators of the medical state observed in biological samples from the patient, which can be measured accurately and reproducibly, indicating normal or pathogenic biological processes (Strimbu and Tavel 2010). Examples of biomarkers include everything from simple pulse rate, and blood pressure, through exhaled gases basic blood chemistries, to more complex laboratory tests, such as analysis of sputum samples. Trying to discuss in details every type of biomarker in association with uncontrolled asthma is beyond the scope of this thesis. A brief overview of the most common inflammatory markers used to monitor disease control in clinical practice is provided in this section.

Collection and analysis of sputum (spontaneous or induced) is a commonly used laboratory-based test for assessing directly the numbers of eosinophilic cell types, reflecting levels of airway inflammation (Wadsworth et al. 2011). Sputum sampling reflects biofluid in the central airways, rather than the peripheral and lower airways (Rutgers et al. 2000). Induced sputum is obtained by the inhalation of nebulized hypertonic saline to trigger sputum production (Wadsworth et al. 2011). The sputum is then coughed out along with any inflammatory cells, which are present in the airway lumen.

It has been indicated that eosinophils in induced sputum are elevated in patients with asthma compared to healthy individuals. (Wark and Gibson 2003; Boot et al. 2007). Increased sputum eosinophils counts have been found to be associated with asthma severity, but weak correlations between sputum eosinophils and asthma symptoms have been reported (Boulay and Boulet 2013). This may be because induced sputum is likely to induce a local inflammatory response generating epithelia and mast cells. This, in turn, can raise doubts about the actual level and progress of airway inflammation in patients with well-controlled asthma. Evaluation of sputum is not commonly performed in routine clinical monitoring of asthma control. This may be because it is mainly a laboratory test, requiring time and experienced personnel. Furthermore, induction, collection and analysis of sputum is a timing consuming process and can be performed differently across different clinical settings, due to a lack of a standardised procedure (Quirce et al. 2010).

To date, a less invasive technique is commonly used in clinical settings to assess levels of airway inflammation. This is the measurement of a surrogate biomarker known as Fractional exhaled Nitric Oxide (FeNO) in breath samples. This biomarker has been found to be correlated well with sputum eosinophil counts (Snell and Newbold 2008; Schleich et al. 2010). The FeNO is a gaseous molecule, which is produced by epithelial cells of bronchial wall. There is conflicting evidence regarding how well this biomarker can reflect asthma control. A study by Bora et al. (2011) examined potential associations between the FeNO and the ACT in a sample of 83 patients with moderate to severe asthma. Results showed weak correlation between the FeNO and asthma symptoms either at baseline measurement or after a 3-month follow-up. Similar results have been found by Leblanc et al. (2007) and Shiota et al. (2011) despite the use of larger sample sizes compared to the study by Bora et al (2011). On the contrary, other studies, which determined uncontrolled asthma by using number of exacerbations, rescue medication usage, or the ACQ_{7item}, have documented high levels of FeNO to be associated with uncontrolled asthma (Ozier et al. 2011; Volbeda et al 2013). These conflicting findings may be therefore related to the different methods used in each study to differentiate patients with different asthma control.

In addition, the FeNO measurements have been also reported to be associated with asthma control in specific patients, such as those treated with low doses of ICS (Michils et al. 2008). This may be because FeNO levels have been found to be reduced after the administration of high doses of ICS, causing doubts regarding its relationship with asthma control in patients with persistent symptoms. Evidence has further showed that the FeNO measurements vary within different asthma phenotypes. Increased levels of FeNO have been found to be correlated well with uncontrolled moderate allergic asthma requiring the use of low doses of ICS to manage eosinophilic airway inflammation (Silkoff et al 2005; Zeiger et al 2011; Schatz et al 2014). On the other hand, patients who had uncontrolled non-allergic asthma with neutrophilic inflammation using higher doses of ICS, have been reported with low levels of FeNO (Kostikas et al 2014; Silkoff et al. 2015). Based on the above, concerns may be raised regarding the use of the FeNO to evaluate asthma control in different phenotypically asthma patients. Hence, identification of other physiological markers in relation to asthma control, which are not be dependent on asthma heterogeneity, has been gained attention (Ricciardolo and Silkoff 2017).

2.6.7 The use of biomarkers to guide asthma treatment

The responsiveness of biomarkers, such as the FeNO, has been examined after the use of different doses of ICS, to guide controller medication (Vijverberg et al. 2011; Petsky et al. 2012; Petsky et al. 2018). However, a systematic review by Vijverberg et al. (2011) concluded that adjusting asthma treatment should not be based on the FeNO alone, due to its dependence on the type and dose of ICS in patients with different asthma severity and type of airway inflammation. This was also supported by a later systematic review by Petsky et al. (2012), who evaluated the evidence regarding the use of the FeNO to tailor asthma treatment among patients with different asthma phenotypes, including both eosinophilic and neutrophilic airway inflammation. The authors stated that inflammatory markers, such as FeNO and induced sputum, can respond differently to different types of anti-inflammatory therapies. The use of ICS is likely to be more effective in reducing asthma symptoms in patients with eosinophilic inflammation than those with neutrophilic inflammation (Berry et al. 2007). Nevertheless, a recent meta-analysis by Petsky et al. (2018) showed that when asthma medication is guided by the FeNO or sputum, the asthma exacerbation rate can be significantly lower compared to that derived from adjustments of asthma medication based on lung function measurements.

Despite the above, biomarkers have not been found to respond to adjunctive asthma therapies, such as breathing retraining, as reported by systematic reviews (Bruurs et al. 2013; Freitas et al. 2013) and the largest RCT by Bruton et al. (2018). This is similar to what has been reported for

lung function measurements, raising concerns about the use of these physiological markers to guide this type of treatment.

2.7 Summary of the chapter

The primary goal of asthma management is to achieve optimal asthma control (GINA 2018). To date, there is no consensus about the use of a gold-standard marker to characterise asthma control, as this can be misleading in the asthma monitoring process. This, in turn, can cause underestimation of patients' medical condition and result in the patients' mistreatment. Thus, monitoring asthma control has been characterised as multi-component process including the use of both subjective and objective validated markers (GINA 2018). Evaluating asthma control is performed by the assessment of clinical symptoms of the disease using valid and reliable questionnaires. The ACQ_{7item} and the ACT have been reported as the most widely used tools in clinical practice and research. However, the main limitation of using such questionnaires is their reliance on patients' perception about their medical condition. Some patients' perception can be poor, so the use of objective physiological markers is an important integral part of the evaluation of asthma control.

To date, in clinical practice, the most commonly used physiological markers are lung function measurements and biomarkers. These physiological markers directly reflect the key pathophysiological mechanisms underlying asthma. However, these markers may not always sufficiently reflect acute asthma symptoms. For example, lung function measurements may not be strongly associated with asthma symptom control in patients with mild asthma compared to those with moderate and severe asthma (Boulay and Boulet 2013). This is because significant distortion of lung function may not always be present in patients with mild asthma, especially in young people, during symptomatic period reporting uncontrolled asthma. In addition, assessing lung function via Spirometry is based on the patients' cooperation, which plays a key role in the accuracy of the respective measurements. Ideally, identification of supplemental physiological markers recorded and analysed easily without requiring patients' cooperation, could enhance the objective evaluation of asthma control along with gaining patients' acceptance.

In addition, inflammatory markers, such as the FeNO, are easy to perform in clinical practice, but can be dependent on asthma phenotypes. Therefore, use of easily quantifiable physiological markers, which can be independent of asthma heterogeneity, may further improve assessments of asthma control in clinical practice. Although all the above physiological markers have been reported to be responsive to asthma medication, they are not likely to change after adjunctive asthma therapies, such as physiotherapy breathing retraining. This type of treatment has been

recently recommended as an effective intervention for asthma management (GINA 2018). The identification of an easily quantifiable physiological marker, which is responsive to this type of treatment, could help to optimise selection of patients who can benefit from this treatment as well as improve our understanding about any potential physiological mechanism underlying this treatment. Based on the above, the research presented in this thesis was shaped due to a perceived emerging need for supplemental objective physiological markers to enhance assessments of asthma control in future clinical practice. A potential supplemental physiological marker was considered by the author to be quantifiable components of breathing patterns for reasons explained in the next chapter.

Chapter 3 Breathing patterns: A potential physiological marker in asthma management

Exploring the use of breathing patterns as a physiological marker in asthma management, firstly requires to look at what constitutes a healthy breathing pattern along with the potential factors influencing a range of quantifiable breathing pattern components. Therefore, this chapter begins with an explanation of the control of breathing. It also includes the definition and description of a range of quantifiable components, which comprise breathing patterns. After providing the rationale for considering breathing patterns as a potential physiological marker in asthma management, separate narrative literature reviews using systematic search approaches (presented in Appendix A) were performed. This was to review the literature regarding the use of specific breathing pattern components as a physiological marker in asthma management. The separate narrative literature reviews aimed to identify published evidence regarding the association between these breathing pattern components and asthma control along with their ability to respond to non-pharmacological interventions, such as breathing retraining. Gaps of knowledge were identified, justifying the need to conduct the research presented in this thesis as summarised in the end of this chapter.

3.1 The control and physiology of breathing

The primary function of the respiratory system is to supply the body with adequate oxygen to meet energy production requirements, while maintaining acid-base balance by removing CO_2 (Petersson and Glenny 2014). This is established by the exchange of oxygen and CO_2 in the lungs through the movement of air in and out of them. The main organs of the respiratory system are the lungs, situated within the thorax wall. The thoracic wall (THW) (known also as the thoracoabdominal area- THA) moves as a result of respiratory muscle contraction and relaxation, creating changes in intrathoracic pressures (Euler et al. 1970; Macklem 1988). This in turn allows the gas exchange with the environment.

The THA is composed of the ribcage (RC) and abdomen (AB), which are the two main compartments and are separated by the diaphragm (De Troyer and Estenne 1988). Normal THA movement is characterised by compartmental expansion and relaxation of the RC and the AB during the inspiration and the expiration phases respectively (Macklem 1988). Although the RC moves in parallel with the AB, in theory each of these compartments can have independence in movements (Konno and Mead 1967). The principal respiratory activity during healthy resting

breathing is predominantly diaphragmatic and consists of a steady, rhythmic and regular involuntary inspiratory muscle action at a relatively constant volume of air (Vt) and respiratory rate (RR) (Yuan et al. 2013).

Breathing is controlled by the concerted function of various integral sites, such as chemoreceptors, mechanoreceptors of the lungs and the respiratory centre (Yuan et al. 2013). To maintain control of breathing, the respiratory centre provides a basic cyclical pattern of respiration, which can be altered by central or peripheral chemoreceptors, which are sensitive to changes in pH, arterial oxygen, CO_2 and emotional stimuli from the limbic system via the hypothalamus (Euler et al. 1970; Jennett et al. 1974; Han et al. 1997). Neural outputs are transmitted from the respiratory centre to spinal motor neurones via the descending bulbospinal pathways, which are responsible for the contraction of respiratory muscles. Under unchanged metabolic demands during resting breathing, the pattern of respiration are said to be constant, interrupted sometimes by a long inspiratory effort, known as sigh over time (Shea et al. 1987).

Breathing at rest requires the activation of inspiratory muscles to move and expand the THA (Yuan et al. 2013). The inspiration time is related to the time required for the transmission of neutral output from the respiratory centre to spinal motor neurones for a complete expansion of THA, and the expiration time refers to the time needed from a full expansion of THA to its return in the initial state (Dempsey and Smith 2014). In the absence of pathology, the expiration at rest is generally a more passive process. However, under increased ventilatory demands, expiratory muscles can have a more active effect on breathing characterised by the simultaneous activation of accessory muscles making expiration a more active process (Dempsey and Smith 2014).

Abnormalities in this automatic pattern of breathing can occur as a consequence of changes in metabolic demands due to a physical stimuli (such as exercise), a voluntary effort in association with psychological arousal, or various pathological processes underlying different respiratory diseases (Yuan et al. 2013; Dempsey and Smith 2014). These can have an impact on the rate, length and intensity of neural outputs derived from the respiratory centre. This, in turn, can result in changes in the RR, the Vt, the length of time for lungs needed to inhale and exhale and the THA movements. All the above changes, in turn, can generate an altered pattern of respiration (Tobin et al. 1983b).

3.2 Definition of a healthy breathing pattern

An individual's breathing pattern is a result of the cooperation of various systems and integral sites, such as receptors, neutral pathways, integration sites and vital organs. The phrase breathing pattern is as a generic term with no consensus regarding its definition within the literature.

Therefore, various quantifiable breathing components have being used to characterise either a healthy or a diseased breathing pattern (Tobin et al. 1983a; Tobin et al. 1983b; Loveridge et al. 1986; Benchetrit 2000; Balleza et al. 2007; Romei et al. 2010).

Dixhoorn (1994) described breathing pattern as a complex process of three key respiratory elements such as gas-exchange, timing indices and the THA movements coordinated by the normal function of respiratory muscles. Various attempts have been made over the years to record and quantify these breathing pattern components (Tobin et al. 1983a; Benchetrit et al. 1989; Landers et al 2003; Ragnarsdottir and Kristinsdottir 2006; Parreira et al. 2010). Some breathing pattern components, such as air volume components, the breath frequency, times required for inspiration and expiration phases, and the %RC contributions to a volume of air , have been recorded objectively for research purposes in both healthy and patients with respiratory diseases, such as asthma (Tobin et al. 1983a; Tobin et al. 1883b; Landers et al 2003; Parreira et al. 2010). On the other hand, other breathing components including the rhythm, regularity, depth and route of breathing have often historically relied on clinical observations of health professionals. For the purposes of this thesis, a breathing pattern refers to quantifiable physiological components, such as timing indices and the THA movements, during resting tidal breathing.

3.2.1 Quantifiable breathing pattern components

Tidal breathing refers to the amount of air displaced during inspiration and expiration phase of each breath cycle during spontaneous restful breathing. In the literature, assessment of the amount of air (Vt) has usually been determined by taking the average of breaths over a period of time during resting tidal breathing (Tobin et al. 1983a; Landers et al. 2003; Parreira et al. 2010; Dellaca et al. 2015). A wide range of normal Vt values have been proposed in the literature due to several factors discussed in the following sections. This in theory may have led to the lack of standardised normative values of Vt, which could be used to assess respiratory health in comparison to well-standardised lung function measurements obtained by Spirometry.

The breath frequency (known also as respiratory rate -RR), is one of the key timing components of a breathing pattern. It is the number of breaths taken over time (usually in one minute). Its maintenance within an optimal range is dependent on the regulation of arterial pH and CO_2 (Cretikos et al. 2008). This breathing pattern component has been therefore characterised as a broad indicator of respiratory stability (Alia and Esteban 2000). It is one of the most easily quantified breathing pattern components, accessible to the majority of health professionals. For instance, at the bedside, the RR can be quantified by using simple fifteen, thirty or sixty second

counts. This can be performed by visual assessments of the RC expansion during inspiration phases of breath cycles.

In the literature, several ranges of the RR have been documented in healthy adults during resting breathing and are reported in more detail in section 3.3 of this chapter. However, an average RR of 12-15 breaths per minute (bpm) has been generally characterised as normal during resting breathing in healthy adults (Hough 2001). Since the magnitude of any metabolic demand can be reflected in changes of the RR, its regular estimation can be used to assist the identification of patients at risk of serious adverse events, especially in intensive care patients. A prospective observational study of 1025 intensive care patients showed that a RR >20 bpm is likely to be predictive of cardiopulmonary arrest within 72 hours and death within 30 days (Hong et al. 2013). Therefore, estimation of the RR has been considered as a vital respiratory sign in the intensive care settings or during the weaning- off process from mechanical ventilation (Alia and Esteban 2000). However, its evaluation in isolation can be misleading. This is because changes in the RR can be attributed to a variety of different respiratory and non-respiratory conditions, such as emotional factors (Masaoka and Homma 1997; Masaoka et al. 2003; Homma and Masaoka 2008). This, in turn, has resulted in a lack of confidence in the clinical use of the RR in isolation as a physiological marker to monitor the presence of asthma. However, changes in the RR have been commonly reported during symptomatic periods of asthma (discussed in section 3.4.1).

Other timing indices, such as the inspiration time (Ti), the expiration time (Te) and measures of the proportionality of them (Ti/Te or Ti over total breath cycle duration- Ttot) can be quantified. This is to provide information about the respiratory phases within a variety of breath cycles taken over time (Alia and Esteban 2000; Aliverti and Macklen 2001; Parreira et al. 2010; Niewoehner 2010). The Ti refers to the time during which air is actively inhaled in the lungs, as a result of the THA expansion during the inspiration phase, whereas the Te refers to the time when air leaves the lungs, due to the passive THA relaxation (resting breathing) or any active expulsion (during exercise or ill-lung conditions) (Parreira et al. 2010). Evidence has shown that the patients with obstructive pulmonary problems appear altered expiration phase, which may attributed to the level of airway obstruction, making it more difficult to breathe out (Niewoehner 2010). However, to date, there is paucity of rigidly defined normative cut-off values not only for the Te, but for all the other timing components, comprising a breathing pattern.

The estimation of the Vt and the timing parameters can be derived by non-invasive recordings of the THA movements through the simultaneous measurement of the compartmental motion of the RC and the AB. The THA refers to the structures on the outside of the body, which surround the lungs and move as the lungs fill and empty (Seddon 2015). There are several non-invasive

recording methods for quantifying compartmental motions of the THA without requiring patients' cooperation. These are outlined and discussed in more detail in chapter 4 of this thesis. Monitoring breathing mechanics may help to evaluate patterns of any pathological THA movements, such as asynchrony or excessive displacement of the RC compared to the AB, in patients with respiratory problems. Traditional recording methods, such as Spirometry, cannot acquire this information. For example, it has been reported that during healthy resting breathing, individuals' total THA movement is attributed to the greater use of the AB compartment, whereas this can change in patients with obstructive respiratory problems who may adopt an upper thoracic breathing (predominant RC motion) (Dechman and Wilson 2004).

The quantification and assessment of the motion of different compartments of THA has not yet been introduced into routine clinical practice as a physiological sign for evaluating progress of respiratory diseases. This may be due to the lack of validated equipment, which can be suited to a clinical environment for measuring these breathing components. To date, the available monitoring methods quantifying the THA movements are primarily laboratory based, and are mainly used for research to characterise breathing mechanics under different recording conditions (Clarenbach et al. 2005; Parreira et al. 2010; Dellaca et al. 2015). There is also a lack of standardised normative values for the RC and the AB displacements during resting breathing, due to the presence of several recording technologies (Fiamma et al. 2007; Levai et al. 2012; Dellaca et al. 2015). These recording technologies use different measurement principles and different anatomical sites to define and quantify movements of the two main compartments of THA.

3.3 The complexity of a breathing pattern

Breathing pattern is a complex, multicomponent process, which is likely to show some degree of variation over time (Tobin et al. 1985). This is because it can be both under voluntary and involuntary control. Although breathing is mainly regulated by the brain stem and is responsive to respiratory metabolic demands, it is possible to voluntarily control our breathing (for example by holding a breath). However this can be performed only for a finite time. It is also documented that behavioural or psychological factors such as anxiety, anger, fear, pain can contribute to changes in several breathing pattern components such as the Vt and the RR during resting breathing (Homma and Masaoka 2008). For instance, anxiety has been shown to change breathing pattern components resulting in a shorter Te and an increased RR (Masaoka and Homma1999). Hence, changes in some breathing pattern components should be interpreted with caution, as they may not always reflect changes in biomechanical or physiological aspects of the respiratory system related to pathophysiological mechanisms underlying the respiratory diseases.

In the literature, attempts at quantifying healthy breathing pattern components have been made under several recording conditions during resting breathing (see Table 3-1 and Table 3-2). Different recording conditions involve different postures, monitoring methods and age groups. These breathing pattern studies have documented several factors, which can have an influence on breathing pattern measurements and further contribute to their complexity. This may have led to the lack of well-defined cut-off values for all the components, which comprise a healthy breathing pattern. This lack of well-defined cut-off values for normal breathing pattern components may also be due to the different methodologies applied in several studies to record and examine a limited number of quantifiable breathing pattern components (see Table 3-1and Table 3-2). In the following sections, some of the most commonly documented factors, which can have an impact on several breathing pattern components, are presented before discussing breathing pattern changes in asthma and their potential use as a physiological marker in asthma management.

3.3.1 The effects of the age on healthy breathing patterns

An early study by Tobin et al. (1983a) reported that people aged ≤50 years old have a more regular stable breathing pattern over time than older people (≥60 years). However, age was not found as a factor to influence absolute measurements of the RR and other timing components such as the Ti. This is in agreement with later studies which have reported a lack of association between timing parameters and the age of healthy adults despite using different monitoring tools and postures to quantify these breathing pattern components (Ragnarsdottir and Kristinsdottir 2006; Parreira et al. 2010; Romei et al. 2010). In theory, the RR and other timing indices have been considered as a relative stable breathing component within individuals of different age groups, as long as respiratory metabolic demands are maintained the same under different recording conditions (Landers et al. 2003).

In contrast, variations in the Vt have been attributed to individuals' age. It has been documented that increasing age is associated with a decrease of the Vt among healthy individuals (Parreira et al. 2010). A normal range of the Vt between 383 ml and 441 ml has been found in small observational cross-sectional studies including healthy individuals (Janssens et al. 1999). However, it has been suggested that differences in the Vt among different age groups may be attributed to decreased lung compliance and elastic recoil during ageing (Parreira et al. 2010). Reductions in lung elastic recoil can limit lungs' ability to be maximally inflated and deflated, thereby restricting the Vt to a narrower range.

Table 3-1: Overview of air volume and timing components of breathing pattern in healthy adults among different ages, postures and gender

Study	Sample size	Age (years)	Gender	Equipment	Posture	Vt* (ml)		RR* (bpm)		Ti* (sec)	Te* (sec)	Ti/Ttot*	
Davis and Stagg (1975)	15	22-63	Both	PNT*	supine	400-900		NR~		1.0-2.5	2.0-3.5	NR*	
Tobin et al (1983a)	47	≤50	Both	RIP*	supine	383		16.7		1.60	NR	0.424	
	18	≥60				382		16.6		1.67		0.413	
Landers et al. (2003)	30	23	Both	PNT	Sitting (slumped posture)	558		14.3		NR	NR	NR	
					Sitting (ribcage fully lifted upward)	650		14.2		NR	NR	NR	
Parreira et al. (2010)	104		Both	RIP	supine	M*	F*	M	F	NR	NR	M	F
		20-39				441	325	13	15			0.42	0.39
		40-59				325	309	16	14			0.41	0.39
		60-80				383	283	15	15			0.39	0.38
Romei et al (2010)	34	32 (22-52)	Both	OEP*		M	F	M	F				
					Sitting	700	500	15.2	16.7	NR	NR	NR	
					Supine	500	400	16	16.6	NR	NR	NR	
Dellaca et al. (2015)	16	28	Both	OEP	Sitting	516		NR		NR	NR	0.39	

*__PNT:__ Pneumotachograph; **NR**: Not reported; **RIP**: Respiratory Inductive Plethysmography; **M**: Male, **F**: Female, **OEP**: Optoelectronic Plethysmography; **Vt**: Tidal volume; **RR**: Respiratory rate; **Ti**: inspiration time; **Te**: Expiration time; **Ti/Ttot**: Measure of proportionality of inspiration time over total breathing cycle duration

Table 3-2: Overview of thoracoabdominal (THA) movements in healthy adults among different ages, postures and gender

Study	Sample size	Age	Gender	Equipment	Posture	THA movements	
Tobin et al. (1983a)	47 18	≤50 (20-50) ≥60 (60-81)	Both	RIP*	Supine	%RC**:42 %RC**:46	
Ragnarsdottir and Kristinsdottir (2006)	100	20-69	Both	RMMI*	Supine	M* RA**:7.47 LA**:7.33 RUTH˜:2.64 LUTH˜:2.66	F* 6.49 6.20 2.64 2.66
Parreira et al. (2010)	104	20-39 40-59 60-80	Both	RIP	Supine	M %RC 39 %RC 32 %RC 37	F %RC 46 %RC 40 %RC 45
Romei et al. (2010)	34	32 (22-52)	Both	OEP*	Sitting Supine	M %RC 76.0 NR	F %RC74.2 NR
Dellaca et al. (2015)	16	28	Both	OEP	Sitting	RCp#: 0.21 AB# : 0.20	

*__RIP__: Respiratory Inductive Plethysmography; __NR__: Not reported; __RMMI__: Respiratory Movement Measuring Instrument (Elite system, ReMO, Keldnahult, Iceland); __M__: male; __F__:female; __OEP__: Optoelectronic Plethysmography; * __RC__: relative ribcage contribution to tidal volume (Vt) expressed in %; **__RA__: Right abdominal motion expressed in mm; __LA__: Left abdominal motion expressed in mm; __RUTH__: Right upper thoracic motion expressed in mm; LUTH: Left upper thoracic motion expressed in mm; # __RCp:__ Ribcage contribution to tidal volume defined as the part of the chest wall between the clavicular line and the horizontal line at the level of the xiphoid process measured in arbitrary units; __AB__: Abdominal contribution to tidal volume defined as the magnitude of displacement of the area between the costal margin and the anterior superior ilia

Moreover, Ragnarsdottir and Kristinsdottir (2006) have reported a 10% decrease in motion of the lower thoracic area in healthy adults aged between 60 and 69 years, in comparison with those aged between 20 and 29 years. However, the reported differences in the THA movements among different age groups found in the study by Ragnarsdottir and Kristinsdottir (2006) were not statistically significant. Lack of significant results may have been due to the presence of small sample size (n=10) in each age group included in the study. Nevertheless, in a larger study (104) by Perreira et al. (2010), it was reported that the percentage RC and AB contribution to Vt did not significantly differ among different age groups, but there were distinct differences in their standard deviations (sd) among all studied age groups. Thus this may denote the presence of different variability of these breathing components.

In contrast, a more recent study by Mendes et al. (2015) examined the effects of age on several components of breathing patterns in 83 healthy adults using the Optoelectronic Plethysmography (OEP). This recording technology is a motion-analysis system of the THA and is explained in more details in chapter 4 of this thesis (section 4.3.1). An association between the age and the THA motion was found with the results from a linear regression analysis showing a decrease of 0.20% in the RC contribution to Vt and an increase of 0.29% in the AB contribution to Vt within a year of age. However, at present, there is a lack of understanding to what level of differences in these breathing pattern components are clinically meaningful, causing doubts about the clinical importance of such degree of change in the THA movements as reported by Ragnarsdottir and Kristinsdottir (2006) and Mendes et al. (2015).

3.3.2 The gender and posture effects on healthy breathing patterns

It has been documented that there may be differences in quantifiable breathing pattern components due to the gender differences between males and females (LoMauro and Aliverti 2018). Although changes in timing components have not been reported due to gender, differences in the Vt and the THA movements have been mainly reported (Romei et al 2010; Parreira et al. 2010). This may be because there are anatomical structural differences between men and women, as observed by chest radiographs and 3-dimensional geometric morphometric recording methods (Bellemare et al. 2003; Torres-Tamayo et al. 2018). For example, men are likely to have larger lungs and longer nasal cavities than females of the same body size, resulting in morphological differences of the upper airways (Garcia-Martinez et al. 2016). Since males have larger lungs, the alveolar surface area is likely to be larger than that of females. Adult males are more likely to have larger Vt during resting breathing than females for a given age and stature. The dimensions of the RC compartment of THA are reported to be wider in men compared to

women, which in turn can result in a greater change of volume in the RC compartment (Shi et al. 2014).

In addition, the percentage RC contribution to Vt in females has been found to be higher than in men during resting breathing (Romei et al. 2010). This is more evident in the sitting position, as significant differences in the percentage RC contributions to Vt between men and women have not been reported in supine position (Verschakelen and Demedts 1995). The differences between males and females being found only in the sitting position, may be attributed to the greater inclination of the ribs in females (LoMauro and Aliverti 2018). This in turn may put the inspiratory RC muscles at a better mechanical advantage. For example, it has been indicated that the more declined the ribs are, the more efficient are the intercostal muscles at raising the ribs, thereby generating more thoracic breathing (Ratnovsky and Elad 2005).

Besides of the gender effect, posture has been documented as another potential factor related to variation in the THA movements among healthy individuals. Romei et al. (2010) examined THA movement changes in both sitting and supine position in 34 healthy adults during resting breathing using the OEP. Authors found that Vt values were highest in the sitting position compared to supine position, with men presenting greater Vt values than women. The authors also reported that posture significantly changed the percentage AB contribution to Vt, as it was found to increase from sitting to supine position. Despite the reliance of these results on a small sample size of an observational study, similar results have been reported by larger observational studies, irrespective of the recording tool used in each study (Perreira et al. 2010; Kameko and Horie 2012).

The reported increase in the percentage AB contribution to Vt occurring in the supine position compared to sitting posture, may be attributed to the elastic properties of the RC and the AB compartments of the THA. While seated, the abdominal content stretches statically the abdominal wall, and so it may limit the further displacement of the diaphragm-abdominal wall due to a fixed abdominal compliance and its elastic properties during resting breathing (Barnas et al. 1993). The weight of the abdominal contents tends also to shorten the fibres of the diaphragm in the sitting position, which in turn can result in a mechanical disadvantage for the AB circumference compared to the RC.

3.3.3 Summary of breathing pattern complexity and variability

The term breathing pattern is an ill-defined generic term, which comprises elements relating to volume components, timing parameters and the THA movements. To date, well-defined cut-off values for normal quantifiable breathing pattern components under different recording

conditions have not been clearly determined in healthy adults, apart from the RR. This may be because of the complexity surrounding measuring breathing patterns, and their variability among individuals. This in theory may have contributed to the lack of their clinical use as a standardised physiological marker in routine clinical practice apart from the lack of a clinical adjustable equipment for their accurate quantification.

In addition to the inter-individual variability of breathing pattern components, evidence has also suggested that there is some degree of intra-individual variability of breathing pattern components (Benchetrit 2000). This consists of structured intra-individual variability and some random variability to ensure stability and adaptability of the respiratory system over time (Benchetrit et al. 1989; Yang 1992; Benchetrit 2000). An early study by Shea et al. (1987) examined 41 healthy adults twice per day over two consecutive days to examine the reproducibility of several breathing pattern components such as the Vt, the RR, the Ti and the Te. These breathing pattern components were measured under the same conditions using the Respiratory Inductive Plethysmography (RIP). This monitoring method is discussed in detail in chapter 4 of this thesis. Briefly, this is a non-invasive motion analysis method, which separately quantifies the circumferential RC and AB displacements to measure a range of breathing pattern components (Clarenbach et al. 2015).

Shea et al. (1987) stated that individuals tend to breathe in a reproducible way over time as determined by the stability of the reported values of all examined breathing components across the recording sessions. Stability was determined by the coefficient of variation (CoV) expressed in a percentage (%). The time intervals between the recording sessions were not reported in this study and the reliance on these results was based on only 24 breath cycles for each individual at each recording session. However, similar results have been reported by Benchetrit et al. (1989) who also found that within-individual reproducibility of breathing patterns can be maintained over longer periods, such as 4-5 years. This is possible as long as the respiratory health of individuals does not change. However, less clear is whether other factors, such as age or posture, can have an impact on within-individual variability of several breathing pattern components over time. Most studies on these factors were looked at in relation to the mean values of breathing components among healthy populations.

Since breathing patterns have been reported to relatively stay stable within individuals, they may be suitable to be used as an indicator of the respiratory diseases, such as asthma (Raoufy et al. 2017). This is because any alteration in the dynamics of this process, which causes either too much or too little regularity in breathing patterns over time, can potentially indicate changes in the respiratory system, due to a respiratory problem (Frey et al. 2011; Raoufy et al. 2016).

Moreover, differences in several breathing pattern components have been reported between healthy people and patients with asthma, even though their relation to disease progress is limited at present. This is discussed in the following sections (sections 3.4.1 and 0). Thus, monitoring and analysis of quantifiable breathing pattern components and their changes over time may provide a better insight into the adaptability of the respiratory system in the presence of a respiratory disease, such as asthma.

3.4 Breathing pattern disorders in asthma

Breathing pattern disorders have been reported as a potential co-existing problem in uncontrolled asthma, even though their actual relationship (causal or coincidental) has not been clearly determined yet (Agache et al. 2012; Veidal et al. 2017). Several definitions to describe breathing pattern disorders have been proposed in the literature. This includes the term of dysfunctional breathing (DB) (Morgan 2002; Thomas et al. 2005; Courtney 2009), hyperventilation syndrome (Burton 1993; Howell 1997), disproportionate breathlessness (Howell 1990) and unexplained dyspnoea (Courtney et al 2011). Although these terms are not precisely the same or usable interchangeably, the term DB has become the most commonly used in clinical practice and the literature (Jones et al. 2011; Barker et al. 2013; Barker and Everard 2015, Courtney 2017). In general, DB has been characterised as a change in the biomechanical and physiological aspects of breathing, which can result in intermittent or chronic respiratory and non-respiratory symptoms (Barker and Everard 2015).

Non-respiratory clinical features of DB include dizziness, altered vision, tingling, numbness, nausea, chest pain and loss of concentration (Howell 1997; Morgan 2002). The most commonly reported respiratory symptoms of the DB are irregular or increased RR, predominant upper thoracic breathing, the THA asynchrony, breathlessness, frequent and deep sighing and wheezing (Prys-Picard et al. 2006; Courtney et al. 2011; Baker and Everard 2015). However, most of the above respiratory features have been traditionally described subjectively through clinicians' observations or symptom questionnaires, exposing the need for using validated objective monitoring methods to directly quantify these features.

The pathophysiology behind the DB in the presence of asthma has been attributed to several mechanisms, which may not always be correlated to each other (Courtney et al. 2011). Patients with asthma are more likely to hyperventilate than the healthy individuals, as evidenced by the presence of hypocapnia (low levels of arterial CO_2) and altered pH (Barker and Everard 2015). This respiratory alkalosis can result in changes to the control of breathing triggering respiratory symptoms characterising the DB. However, the relationship between respiratory symptoms of the

DB and hypocapnia is not clear. Patients with asthma and fixed-hypocapnia have been reported not to have always symptoms of the DB (Boulding et al. 2016). Psychological factors, such as anxiety, have been considered as another trigger for the DB, as emotional arousal can have an effect on control of breathing (Ritz 2012). Current evidence has reported that there is higher than normal prevalence of anxiety in the asthma population (Ritz et al. 2013).

On the other hand, there may be biomechanical alterations underlying the DB. These refer to patients who display a lack of predominant diaphragmatic breathing, replaced by upper thoracic breathing during resting breathing (Courtney et al. 2011; Barker and Everard 2015). Another characteristic of the DB has been described to be paradoxical THA movements, according to which the AB is drawn in rather than outward during the inspiratory phase, resulting in asynchrony with the RC motion (Courtney et al. 2008). This thoracic dominant breathing has been suggested to be a normal response to an increase in the respiratory demand and the altered respiratory drive occurring during symptomatic periods of asthma. This, in turn, may lead to an increase of the neural output to inspiratory muscles, which can become shortened and hypertonic, thereby changing breathing mechanics (Peper and Tibbetts 1994). However, the data on breathing pattern components and the DB are mostly derived from the clinician's observations, so there is a need to objectively monitor and quantify breathing pattern components to explore their actual relationship with the presence of DB within uncontrolled asthma.

In clinical practice, the presence of DB in asthma patients is conventionally evaluated by the use of a subjective questionnaire, known as the Nijmegen Questionnaire (NQ) (Boulding et al. 2016; Vidotto et al. 2019). One of the creators of this questionnaire has recently stated that although the NQ was first developed to assess presence of hyperventilation, it is a tool that can be used to reflect a subjective aspect of the DB (Dixhoom and Folgering 2015). The NQ was first validated in people with exercise-induced hyperventilation (Van Dixhoorn and Duivenvoorden 1985). Since then, its use has evolved to describe the presence of DB, and not just metabolic hyperventilation (Baker and Everard 2015). This questionnaire comprises of seven items related to respiratory symptoms, four items related to excessive ventilation and five items related to central nervous system's symptoms relating to hypocapnia (Van Dixhoorn and Duivenvoorden 1985). A NQ score ≥23 conventionally indicates the presence of DB in clinical practice (Courtney et al. 2011; Boulding et al. 2016). However, lower scores do not exclude the possibility of presence of DB (Grammatopoulou et al. 2014; Dixhoom and Folgering 2015).

Although this questionnaire can be easily-administered in clinical settings, it relies on patients' perceptions of their breathing. Since patients with asthma are susceptible to emotional arousal, this may contribute to an erroneous perception of their altered breathing during symptomatic

periods of asthma (Ritz et al. 2013). Given the multidimensionality of breathing, a questionnaire of this type may not seem be sufficient to detect DB, and its use in conjunction with other objective physiological outcomes is now recommended in clinical practice (Vidotto et al. 2019). Although difference in quantifiable breathing pattern components have been reported in the asthma literature, limited body of evidence has studied the actual relationship between these breathing pattern components and asthma control along with their ability to be used as a surrogate marker of DB.

3.4.1 Changes in quantifiable components of breathing patterns in asthma patients

Quantifiable breathing pattern differences have been documented in patients with asthma compared to healthy adults (Kassabian et al. 1982; Hillman et al. 1986; Tobin et al. 1983b; Kesten et al. 1990; Courtney 2009) and among asthma patients during induced bronchoconstriction (Ringel et al. 1983; Lennox et al. 1985; Gorini et al. 1999;Lavorini et al. 2013). Structural bronchial changes (known as airway remodelling) causing reversible airflow limitation and fixed airway obstruction have been suggested as some factors for the changes in quantifiable breathing pattern components in asthma (Ringel et al. 1983; Gorini et al. 1999; Courtney 2009; Lavorini et al. 2013). The table below provides an overview of the mean values of several quantifiable breathing pattern components in adult patients with asthma, as compared to healthy adults during resting breathing, or after induced bronchoconstriction.

An early study by Kassabian et al. (1982) compared several breathing pattern components between healthy adults (n=17) and patients with severe asthma (n=17). The authors reported that mean values of the Vt, the RR, the Ti and the Ti/Ttot were significantly different between groups. The reported differences in breathing components were speculated to be due to changes in respiratory drive output. This can modify breathing patterns to adapt increased metabolic demands in the presence of hyperventilation. The authors did not take direct physiological measurements of the CO_2, and their findings were based on an increase in the minute ventilation within the majority of the asthma patients during resting breathing. It is worth to mention that the authors used invasive recording equipment (pneumotachograph-PNT) to monitor breathing. This equipment requires the use of a mouthpiece or facemask to record breathing, which have been reported to change an individual's natural breathing pattern (Perez and Tobin 1985). This could therefore affect the accurate interpretation of any potential breathing pattern differences seen between groups in the study by Kassabian et al. (1982) and any reported cause of the results by them.

Irrespective of the above methodological limitations, similar results have been reported by Tobin et al. (1983b). The authors used a non-invasive recording equipment (RIP) to obtain breathing pattern measurements from healthy adults and both symptomatic and asymptomatic patients with asthma. Although significant differences in breathing patterns were not found between healthy group and asymptomatic patients, a significant increase in the Vt was reported in the symptomatic patients who were also reported to have airflow limitation ($FEV_{1predicted}$ 61%). However, no statistically significant differences in any of the examined components, such as the RR, the Ti/Ttot and the percentage RC contribution to Vt, were found among the groups, possibly due to the small unequal groups included in the authors' study.

On the other hand, studies applying induced bronchoconstriction causing greater airflow limitation ($FEV_{1predicted}$: 40% to 50%) than that observed naturally by Tobin et al. (1983b), have showed a significant increase of the RR, decrease of the Ti/Ttot and asynchrony between the RC and the AB motion (Ringel et al. 1983; Lennox et al. 1985, Gorini et al. 1999). This can therefore suggest that changes in timing components and breathing mechanics may not be easily detectable during asymptomatic periods compared to symptomatic periods in the presence of major decline of lung function. This theory has further supported by Kesten et al. (1990), who examined differences in the RR and the Vt among three different groups of patients with different asthma severity having variable airflow limitation.

The authors recruited 47 acutely ill severe asthmatics in an emergency room, 9 asymptomatic moderate asthma patients during methacholine challenge, and 8 patients with mild asthma during exercise-induced bronchoconstriction. Despite the unequal small number of subjects in each of the examined groups, differences in breathing patterns were reported across all groups. However, a statistically significant increase in the RR and the Vt was only reported in the acutely ill patients compared to the other groups. The authors concluded that differences in breathing pattern components could be attributed to the variable decline of lung function, which was present among patients with different severities of asthma. This was hypothesised by the presence of variable airflow limitation caused by a methacholine challenge or exercise, which were different from that resulting from acute asthma exacerbation in severe patients. This, in turn, could result in the variable behaviours of the examined breathing pattern components among the studied groups.

Table 3-3: Overview of the quantifiable components of breathing patterns in healthy adults compared to patients with asthma or among patients with asthma during or after bronchoconstriction

Study	Recording Condition	Equipment	Studied population	Vt (ml)	RR (bpm)	Ti (sec)	Te (sec)	Ti/Ttot (sec)	%RC contribution to Vt
Kassabian et al. (1992)	S˜RB~	PNT~	17 asthmatics 17 healthy	590 650	22 15	1.05 2.05	NR~ NR~	0.38	NE~ NE~
Tobin et al. (1983b)	SP˜RB~	RIP~	17 AAP~ 15 SAP~ 47 healthy	386 679 383	16.6 16.0 16.6	1.62 1.55 1.62	NR NR NR	0.42 0.37 0.42	55 51 42
Lennox et al. (1985)	S~ RB~ S~ after BC~	RIP	7 asthmatics	700 920	18.7 20.8	1.37 1.07	2.03 1.86	0.41 0.36	NR~ NR~
Gorini et al. (1999)	S~ RB~ S~ during BC~	ELITE~	7 asthmatics	800 920	14.8 15.2	1.60 1.40	2.7 2.8	NR NR	NR NR

~ **S:** sitting position; **RB:** resting breathing; **SP:** supine position; **PNT:** Pneumotachograph; **NR:** Not reported; **NE:** Not examined; **RIP:** Respiratory Inductive Plethysmography; **APP:** Asymptomatic asthmatic patients; **SAP:** symptomatic asthmatic patients; **BC:** bronchoconstriction; **ELITE:** optical reflectance motion analysis system

Although there can be variable respiratory behaviours among patients with asthma, recent observational studies have reported that patients with acute persistent asthma tend to adopt a rapid, predominantly thoracic breathing during resting breathing without being rigorously examined if this occurs in the presence of uncontrolled asthma (Courtney et al. 2011). This is accompanied by variable and reversible airflow limitation, to adopt altered metabolic demands (Lavorini et al. 2013; Foumani et al. 2015). Thus, changes in quantifiable breathing pattern components may provide a physiological insight into the function of the respiratory system in asthma during symptomatic periods.

3.5 Quantifiable breathing pattern components in association with asthma control

Although quantifiable breathing pattern components have been reported to change in asthma compared to healthy individuals, to date there is limited body of evidence examining their association with asthma control. This in turn has caused ambiguity regarding their role in asthma management. At present, breathing pattern changes in asthma have been mainly assessed via the examination of associations between the DB and asthma control (Courtney et al. 2011; Veidal et al. 2017, Denton et al. 2018). Evidence has reported that uncontrolled asthma (as measured via questionnaires such as the ACQ_{7item}) is related to DB as detected by the use of the NQ (Courtney 2017). However, as mentioned previously, the NQ reflects a subjective perspective of altered breathing. This provides no evidence of changes in any quantifiable breathing pattern components, as the research presented in this thesis aimed to explore.

According to a narrative literature review performed by the author initially between November 2016 and December 2016, updated between September 2017 and October 2017 and between April 2019 and May 2019, there is a paucity of data regarding the use of quantifiable breathing pattern components as a physiological marker of asthma control. Those few studies that have been published have several methodological limitations, resulting in no firm conclusions. Some of the limitations include small sample sizes, lack of examination of variable breathing pattern components, and use of different tools for quantifying asthma control.

An early study by Filippelli et al. (2003) examined the relationship between the Vt (as measured by the sum of the RC volume and the AB volume, using the OEP) and breathlessness (determined by the use of the Borg scale). Breathlessness is considered as a common asthma symptom during loss of disease control (Wong et al. 2016). The results of a linear regression analysis obtained by breath-by-breath analysis from 8 clinically stable people with asthma during a methacholine

challenge showed that increased breathlessness was correlated to an increase in the Vt derived from RC circumferance, explaining 47% of the variance in the Borg scale. However, using only one symptom to determine asthma control after inducing bronchoconstriction may not be sufficient to quantify this multidimensional concept and look at its natural association with only one element of a breathing pattern, such as the Vt.

Upton et al. (2012) have examined the associations between asthma control as measured via the ACQ_{7item} and only a parameter associated with the THA movements. This was the THA asynchrony (TAA) and its association with asthma control were studied in 43 patients with different asthma severity. The TAA was estimated using the RIP as the percentage of time in which the effects of the RC and the AB motion led to opposite effects on intrathoracic volume. Although there was a statistically significant correlation between the TAA and the ACQ scores, this correlation was found to be weak (r=0.33). A post-hoc exploratory subgroup analysis showed that there was a significant correlation between examined variables only in females, but not in males. However, the results of this study should be interpreted with caution due to the small total sample size (n= 43). There was limited sample size of the subgroups included the authors' study, in which examination of associations between variables were sought. The authors reported that the female subgroup was larger than the male one. Furthermore, the majority of the participants reported relatively well-controlled asthma, limiting the variance of the obtained ACQ scores, thereby reducing the opportunity to identify strong associations between the examined variables in the sample.

In comparison with the results reported by Upton et al. (2012), Raoufy et al. (2016) investigated the use of breathing pattern variability as an indicator for asthma control within a single recording session. The authors estimated breath-by-breath fluctuations of the Vt and the length of breath cycles over one hour. This was studied in a sample of 10 healthy individuals, 10 patients with controlled atopic asthma, 10 patients with uncontrolled atopic asthma and 10 patients with uncontrolled non-atopic asthma. Estimates of the Vt were determined as the amplitude of each breath cycle from the trough to peak in a sinusoidal waveform generated by the RIP. The breath cycle length was determined as the peak-to-peak intervals of the signals received by the RIP. Results of the study indicated that patients with uncontrolled asthma (both atopic and non-atopic) had significant differences in the variability of the examined breathing components compared to well-controlled asthma patients and healthy individuals. Furthermore, a receiver operating curve (ROC) analysis showed that variability of examined variables could also differentiate uncontrolled asthma patients from those who were healthy. The ROC curve is a technique to evaluate the diagnostic accuracy of an outcome, in which the true positive rate is plotted against the false positive rate at various threshold settings (Park et al. 2004). However,

only male patients were examined in the study, as a result the existence of the above associations in a wider asthma population could not be determined.

Based on the above limited number of published studies, there was a need for more research to be done to expand current knowledge regarding the use of other quantifiable breathing pattern components as a physiological marker for asthma control. There is a gap in our knowledge regarding the associations between other breathing pattern components, such as timing parameters and their variability over time, and asthma control together with their ability to evaluate asthma control.

In addition, there is diversity among the published studies in terms of breathing pattern measurements. For example, some studies have included single-time assessments, whereas others have focused on their measurements over time looking at their within-individual variability. At present, the optimal breathing pattern measurements to be used as an indicator of asthma control is not known. Hence the research presented in this thesis primarily aimed to examine the use of both absolute measurements and within-individual variability of a range of breathing pattern components, such as timing parameters and the THA movements, as a physiological marker for asthma control.

3.6 The use of quantifiable components of breathing patterns to guide asthma treatment

In addition to there being a small body of evidence surrounding the use of quantifiable breathing pattern components as a physiological marker of asthma control, there is also a paucity of evidence regarding their use as an outcome to guide asthma treatment. Pharmacotherapy is the first line treatment in asthma and well-standardised outcomes (lung function and biomarkers) are currently used to guide treatment plans (Bostantzoglou et al. 2015). As medication aims to alleviate the pathophysiological mechanisms underlying asthma, such as airway inflammation and obstruction, direct markers reflecting these pathophysiological mechanisms have been used to monitor the effectiveness of different pharmacological therapies. Despite receiving appropriate pharmacotherapy, some patients with asthma can benefit from breathing exercises, such as physiotherapy breathing retraining programmes. Breathing retraining has been found to be an effective adjunctive regimen to improve patient-related outcomes, such as asthma-related quality of life (Bruton et al. 2018).

One of the logical theories behind breathing retraining is that it modifies breathing patterns. However, most of the published studies have not examined or reported changes in quantifiable

components of breathing patterns, leaving a gap in our current knowledge regarding their responsiveness to this type of treatment. This is because most of the studies have measured a surrogate marker for breathing pattern changes after breathing exercises, such as the NQ (Thomas et al. 2003; Hagman et al. 2011; Jones et al. 2015; Bruton et al. 2018). A RCT by Grammatopoulou et al. (2011) reported a change in a timing parameter (RR) following breathing retraining. The authors reported a decrease in the RR within the group, which received twelve face-to-face breathing retraining sessions, compared to a control group, who received only standard asthma care. However, there was no report about the responsiveness of any other core quantifiable breathing pattern components, which this intervention has been designed to modify.

Vieira et al. (2014) examined the impact of performing several breathing manoeuvres, including diaphragmatic breathing, on several breathing pattern components, such as the Vt, the RR, the %RC to Vt, and the TAA. Diaphragmatic breathing is a core element of breathing retraining. Breathing pattern components were measured by the OEP. The authors reported changes of all examined components of breathing patterns during diaphragmatic breathing as compared to resting breathing. A decrease in the RR and the %RC to Vt was found during diaphragmatic breathing compared to resting breathing. However, these quantifiable breathing pattern components were examined only in healthy adults, and only while they performed the breathing manoeuvre, giving no information about maintenance of their changes over time.

To date, only one case study by Tehrany et al. (2018) has been published, in which the authors attempted to investigate the responsiveness of several quantifiable breathing pattern components before and after a clinical physiotherapy breathing retraining programme for asthma. A single female patient with asthma received three face-to face breathing retraining sessions over a period of sixteen weeks. Measurements of the RR, the Ti, the Te and the percentage RC contribution to Vt were taken at baseline and on her last day of breathing retraining, during resting and speech breathing using the RIP. However, unfortunately, corruption of the baseline breathing pattern data during resting breathing prevented comparisons with the data taken after breathing retraining. This has left an ongoing gap in the knowledge regarding the responsiveness of specific quantifiable breathing pattern components to this type of intervention posing the need for more research as undertaken in this thesis.

3.7 Summary of the chapter: The rationale for conducting this research

Breathing pattern is a complex umbrella term comprising different quantifiable components, such as volume parameters, timing indices and THA movements (Tobin et al. 1983a; Landers et al. 2003; Parreira et al. 2010). Due to their individuality and continuous fluctuation over time, they

have been considered to provide information about the function of the respiratory system. To date, differences in a range of quantifiable breathing pattern components have been documented between healthy individuals and patients with asthma, and among asthma during bronchoconstriction (Kesten et al. 1990;Courtney 2009; Lavorini et al. 2013). However, their clinical value as a physiological marker in asthma management has not been clearly established.

There is a paucity of evidence regarding the use of timing parameters and the THA movements in relation to asthma control. The research presented in this thesis therefore primarily examined the use of these breathing pattern components as a supplemental physiological marker to predict asthma control when measured on one occasion. Instead of using subjective questionnaires or simple observational methods for breathing pattern measurements, a validated recording technology was deemed to be the suitable method to objectively quantify and analyse both absolute measurements and within-individual variability of the examined breathing pattern components. The limited body of evidence regarding the association of altered quantifiable components of breathing patterns with the presence of DB in asthma led the researcher to secondary look at the use of the examined breathing pattern components of this research as a surrogate physiological marker for DB. In current clinical practice, the presence of dysfunctional breathing is based on the use of a subjective questionnaire, the NQ, which do not provide quantification of elements of altered quantifiable breathing pattern components. So any association between the examined quantifiable components breathing components and the NQ scores was secondary examined in the same study.

Instead of looking only at the associations between the breathing pattern components and some patient-related outcomes used in asthma management, it was also deemed interesting to secondary look at the association between the examined breathing pattern components and lung function measurements. This is a physiological marker used in asthma management and the current literature has indicated changes in breathing pattern components in asthma patients with variable lung function. This stressed the need to additional look at their between relationship. Hence, an observational cross-sectional study was conducted to recruit asthma patients with different level of asthma control and examine the associations between the quantifiable breathing pattern components and multiple clinical asthma-related outcomes used in asthma management. This correlational study is presented in chapter 6 of this thesis.

Understanding the use of quantifiable breathing pattern components as a physiological marker for asthma control can also involve the examination of its ability to be used as a physiological marker of any treatment effect after asthma treatment. This together with a gap of knowledge regarding the response of breathing pattern components to an effective adjunctive asthma

therapy, such as breathing retraining, led the researcher to conduct a responsiveness study in this research. Through this study, changes in the examined breathing pattern components following a clinical physiotherapy breathing retraining programme were examined. This could provide additional information about the use of breathing patterns as a physiological marker in asthma management, which was the overall aim of the research presented in this thesis. It was not possible within this PhD's scope and timeframe to set up and run a full RCT. Therefore, a pragmatic decision was made to conduct an experimental single-arm study with repeated measures to achieve the aim of this responsiveness study. The responsiveness study is presented in chapter 7 of this thesis.

Before conducting the correlational study and the responsiveness study, it was first necessary to identify a validated method for measuring the breathing pattern components of interest for this research. A narrative literature review using a systematic search approach (provided in Appendix A) allowed the researcher to review current validated recording methods for breathing pattern measurements. This is discussed in the next chapter of this thesis.

Chapter 4 Recording and analysis of breathing patterns using valid non-invasive monitoring methods

The validity of any measurement tool refers to its ability to provide accurate estimates of what it is intended to measure (Borsboom et al. 2004). Valid recording methods to monitor lung function, such as Spirometry, are well standardised in clinical practice (Miller et al. 2005). A desirable goal is to be able to monitor breathing from different environments, such as in the home or in ways that are least disruptive to daily life and encourage the patients to adhere to the monitoring process. Non-invasive recording methods have the potential to be acceptable and encourage the patients' adherence to the monitoring process (Folke et al. 2003). The term non-invasive refers to those methods that do not require taking blood samples, using facemasks, mouthpieces or nose clips or requiring patients' cooperation (Folke et al. 2003).

In this chapter, the validity of currently available non-invasive monitoring methods for breathing pattern measurements is discussed. The recording instruments presented in this chapter, were selected due to their widespread documented use as valid monitoring tools in the research. A discussion of the potential pitfalls and advantages for each described monitoring tool is also provided. This chapter concludes with the justification for conducting a preliminary validation study of a new recording method, known as the Structured Light Plethysmography (SLP), prior to determining the recording method used in the subsequent studies of this research.

4.1 An overview of current clinical monitoring methods for breathing patterns in clinical practice

In clinical settings, breathing pattern components are usually evaluated with the patient in a relaxed position, normally in the sitting position, during resting breathing through simple observational techniques (O'Hanlon-Nichols 1998). One of these is the visual assessment of the thoracoabdominal area (THA) movements, which is used to estimate the respiratory rate (RR), and determine the rhythm of breathing (Cox and McGrath 1999). The RR is estimated by noting the frequency of the inspiratory phases as observed by the active expansion of the ribcage (RC) over a period of fifteen, thirty and sixty seconds (Ahern and Philpot 2002). The rhythm of breathing can be assessed by observing the regularity of the same amount of the RC expansion for each breath cycle during resting breathing (Moore 2007). Although these methods are easily performed, they may lack accuracy.

Large tidal volume breaths can be easily counted, whereas rapid shallow breaths can be missed. A recent study by Tulaimat et al. (2016) examined the validity of the clinicians' observational assessment of increased breathing as estimated by the RR in mechanically ventilated patients. Analysis of the ratings of four critical care consultants and four critical care fellows showed poor agreement between their ratings for assessing shallow breathing with the clinicians tending to underestimate the RR. This was possibly due to the irregularity of the undetected small breaths. However, in this study clinicians were given only few seconds (six to ten seconds) to estimate the RR. This could have further contributed to the underestimation of the total number of breath cycles, as a minimum sixty second count has been proposed to be a more accurate observational technique (Hill et al. 2018).

Other simple methods of breathing pattern assessments are based on the clinicians' manual palpation. This can be used to identify paradoxical breathing characterised by the abdomen (AB) moving inwards during the inspiration phase and outwards during the expiration phase (Chapman et al. 2016). A technique known as the Manual Assessment of Respiratory Motion (MARM) has been recently suggested as another simple observational method to quantify breathing patterns in a practical, inexpensive and accurate manner (Courtney et al. 2008). A clinician allocates his/her hands on the posterior and lateral part of the eleventh and twelfth rib with the patient in a sitting posture. During resting breathing, the clinician evaluates the perceived displacement of the upper and lower thorax motion as well as the abdominal expansion. This is estimated by the angle difference between the upper thorax and the lower thorax (Courtney et al. 2008). Through this method, estimates of the RR and the THA movements can be obtained.

In the validation study of the MARM, the authors reported significant correlations (r=0.597) between the observers' MARM estimates and the measurements obtained by the Respiratory Inductive Plethysmography (RIP) (Courtney et al. 2008). The RIP is a motion analysis equipment discussed in detail in section 4.2 of this chapter. However, the authors' findings are based upon a simple correlational analysis, which does not allow the identification of any potential systematic bias between the comparable methods (Bland and Altman 1999). Furthermore, the assessment of the THA movements using the MARM is based on the examiner's perception, and so its use may be of limited to experienced health professionals. For instance, all the observers in the authors' validation study were experienced in their field. The MARM has to be performed in the sitting position, which may also limit its clinical application and accuracy in other postures, such as supine or standing, as it has not been validated in these postures.

Technological advances in microelectronics and signal processing techniques have allowed the development of monitoring technologies, which objectively quantify and analyse a wide variety of

breathing pattern components over time. Early methods to do this were generally invasive and required the use of a mouthpiece, facemask or nose clips to measure pressure changes through which estimates of the tidal volume (Vt) could be obtained (Kreit and Sciurba 1996; Stromberg and Gronkvist 1999). They are considered as invasive recording methods because of the requirement of a direct physical attachment between the examined individual and his airway opening (mouth or nose) (Stromberg and Gronkvist 1999).

Spirometry is the gold-standard invasive monitoring method for diagnosing and managing patients with respiratory diseases such as asthma (GINA 2018). It provides accurate quantifiable measures of lung volumes. Its availability has markedly increased over the past two decades. Spirometry measures the expiratory airflow during a single breath and integrates the measured flow of air to obtain measurements of the FEV_1, the FVC, their ratio, and the PEF (Miller et al. 2005). This occurs via pressure sensors allocated within the spirometers and a pressure drop across a resistance element is calculated. This occurs when air moves from that element. It is an effort-dependent technique, which requires the individuals' cooperation, giving their maximal effort to perform a forced expiratory manoeuvre (Townsend 2011). The forced expiratory manoeuvre involves a maximal deep inspiration, which stretches the RC to its maximum, and then a full forced expiration is rapidly performed and should be maintained for 6 seconds (Hegewald et al. 2016).

Although Spirometry is a well-standardised monitoring tool in clinical practice, the validity of its results depends on both technical and non-technical factors. From a technical perspective, elevated values of lung function measurements can be caused by a "zero-error" problem (Townsend et al. 2004). This type of error can occur when the pressure sensor erroneously measures a pressure gradient, when in fact no air passes through the sensor. As a consequence, an airflow can be falsely detected before an individual's test, resulting in a measurement error and overestimation of lung volumes. The ability of patients to perform optimal expiratory manoeuvres is a non-technical factor for optimising quality of Spirometry measurements (Hegewald et al. 2016). Giner et al. (2014) explored Spirometry measurement errors in relation to patients' characteristics. Results from 136 patients with a diagnosis of an obstructive lung disease showed that the forced expiratory manoeuvre and the patients' lack of experience were the main factors associated with poor Spirometry accuracy. As failure to perform an optimal expiratory manoeuvre can lead to the underestimation of lung function, this recording method may be of limited use for several group of patients, such as the very young or the unco-operative individuals, the critically ill or severe symptomatic patients with or without a parallel cognitive impairment (Giner et al. 2014).

In addition, lung function assessment using Spirometry is made by the recording of a single maximal breath and not by the continuous monitoring of the natural behaviour of breathing over the time (Folke et al. 2003). Monitoring of breathing over time may offer a better understanding and detailed description of its function in respiratory diseases (Seddon 2015). Monitoring alterations or fluctuations of breathing components, such as the THA movements and several timing parameters, cannot be estimated via spirometers. Thus, other monitoring methods have been developed over the years to facilitate the continuous measurement of a range of breathing pattern components over time under different breathing conditions, either in healthy individuals or in patients with respiratory diseases.

4.1.1 Monitoring breathing patterns via the Pneumotachograph

The Pneumotachograph (PNT) is considered to be the gold-standard method for continuous measuring air volume components of breathing patterns over time (Groepenhoff et al. 2011). The PNT is an invasive laboratory-based device and its measurement principle is based on the linearity of airflow to a change of pressure. This is generated by breathing through a mouthpiece into an element of resistance allocated within the equipment (Kreit and Sciurba 1996). Based on this, pressure changes along the length of a tube are proportional to the airflow, which passes in and out the tube (Stromberg and Gronkvist 1999). A mouthpiece or tightly fitted facemask is required to cover an individual's nose and mouth, through which he/she can breathe. Since airflow is assumed to be linearly related to the pressure gradient, this information is processed within the system and can be converted to estimates of the Vt. Doubts regarding the accuracy of the PNT may be raised when the known linear relationship between airflow and pressure change is violated. For example, the condensation of water vapour caused by the different temperature or composition of respiratory gases, can be a factor for violating this linear relationship. To overcome such technical issues, inclusion of a heating element within the PNT is advisable to eliminate the effects of the condensation of water vapour (Tang et al. 2003; Jewitt and Thomas 2012).

The major limitation of this recording method is the use of the facemasks or the mouthpieces. Instrumental-induced changes in quantifiable breathing pattern components have been reported by some validation studies (Dolfin et al. 1983; Perez and Tobin 1985; Patzak et al. 2001). Dolfin et al. (1983) evaluated the potential effect of a facial attachment through a PNT's facemask on breathing pattern measurements compared to the RIP. The RIP records the THA movements using two elasticated bands positioned on the RC and the AB circumference (discussed in section 4.2.2). In the study by Dolfin et al. (1983), significant differences were found in the Vt and the RR when simultaneous recordings of breathing patterns were performed by comparable methods

compared to the RIP measurements used in isolation. However, only healthy infants were examined in this study, so generalisations of these findings to other populations were not possible.

Perez and Tobin (1985) measured the Vt and the RR using the RIP and the PNT in 10 healthy adults during resting breathing. The authors reported a decrease in the RR and an increase in the Vt. This occurred when simultaneous RIP and PNT recordings were taken, compared to measurements obtained by the RIP in isolation. A factor causing these changes has been hypothesised to be the stimulation of the trigeminal area through the facemask use (Bates et al. 2000; Patzak et al. 2001). This anatomical area is a rich sensory area whose stimulation can be caused by the tight attachment of the PNT's facemask (Crenesse et al. 2001). In addition, the tight attachment of a facemask can increase the measured lung dead-space, due to the potential presence of trapped air between the equipment and the individuals' face (Rodenstein et al. 1985; Bates et al. 2000). Another impact of the tight attachment of the facemask to individuals' face has been reported to be a change to the route of breathing (Han et al. 1997). It forces individuals to breathe orally irrespective of the individuals' normal route of breathing, thereby altering the natural behaviour of breathing (Crenesse et al. 2001).

To overcome the above limitations associated with the PNT, various non-invasive methods have been developed to facilitate the recording of natural breathing behaviour over time (Folke et al. 2003). Non-invasive recording techniques use several biosignals. These biosignals provide continuous information about the respiratory activity as illustrated in a sinusoidal waveform (time-trace) over time (Grepl et al. 2015). Typical biosignals are: a) bioimpedance (measurement of the change of impedance of lung tissue), b) biomechanical (measurement of any change in inductance within a cross-sectional area of the THA circumference), c) biochemical (measurement of any change in the concentration of gas in breath or blood), d) bioacoustics (quantification of the breath sounds generated by the flow of air through the respiratory tract), e) bioelectric (monitoring the activity of the respiratory muscles) and f) biooptical (optical measurements of the THA movements) (Folke et al. 2003, Ball et al. 2013, Grepl et al. 2015).

In the following sections of this chapter, a literature review of non-invasive recording methods using biomechanical and optical technologies for breathing pattern measurements is provided. This selection was made based on their widely use in the breathing pattern research. The main assumption behind these recording methods is that the THA motion is related to the volume displacement within the lungs (Folke et al. 2003). By quantifying the THA motion during tidal breathing, it is therefore deemed to be possible to estimate a range of quantifiable breathing pattern components such as a) relative or absolute air volume components, b) timing parameters

(RR, Ti, Te, Ti/Te, Ti/Ttot) and 3) the regional contributions (RC and AB) to both inspired and expired Vt (Ball et al. 2013).

4.2 The Respiratory Inductive Plethysmography

4.2.1 The Konno and Mead Theory (1967)

The RIP is a non-invasive monitoring method, which quantifies the circumferential displacement of the two main compartments of the THA by using biomechanical signals (Martinot-Lagarde et al. 1988). The measurement principles underlying the RIP are based on the Konno and Mead theory (1967). According to this theory, the anterior surface of the THA is a coextensive area divided into two main anatomical regions. These regions are the RC and the AB and their dividing line is the costal margin. Based on observations of the THA motion during resting breathing, a functional difference in motion between the RC and the AB was proposed by Konno and Mead (1967). They proposed that each region behaves as a single independent unit. Thus, they noted that the THA can be an open system which mainly comprises of two independent parts and each of these parts has a single degree of motion.

Based on this theory, the anterior-posterior and radial movements of the RC and the AB were deemed to reflect a single value of volume change within each region. A linear relationship was therefore established between the displacement of each region of the THA and the volume changes occurring within each region. The authors proposed that the sum of the individual volume changes within each region of the THA equals to the changes of the Vt at the opening airways (mouth or nose) (Konno and Mead 1967). This was given in the equation $\Delta Vt_{RC} + \Delta Vt_{AB} = \Delta Vt$ (1) ; where ΔVt is the air volume change occurred in the airway opening, and ΔVt_{RB} and ΔVt_{AB} refer to the air volume changes occurring in the RC and the AB respectively.

4.2.2 The recording approach of the Respiratory Inductive Plethysmography

The RIP uses inductance isolated wire coils sewn in two elastic bands in a zig-zag form to monitor the excursion of the THA (Martinot-Lagarde et al. 1988). One band is located around the RC at the height of the axilla (armpit) and the other is located around the AB at the height of the umbilicus (Tobin 1992, Leino et al. 2001) (see Figure 4-1). Changes in the RC and the AB movements during breathing cause the expansion of the elastic bands. This in turn creates a magnetic field around the circumference of the RC and the AB during the passage of an alternating current through the bands (Martinot-Lagarde et al. 1988). Changes in the shape of this magnetic field result in the generation of an opposing current, which is proportional to the change of the motion of each

region of the THA (Tobin 1992). This opposing current is measured in voltage over time and the different signals are generated by the individual motion of the RC and the AB. This is illustrated as a sinusoidal waveform on a computer screen. Through this, the RIP can allow continuous monitoring of several quantifiable components of breathing patterns such as air volume components, the RR (plus other timing parameters) and the regional contributions of the RC and the AB to Vt (Leino et al. 2001; Clarenbach et al. 2005; Grossman et al. 2010; Cabiddu et al. 2016). This also allows the quantification of within-individual variability of breathing components over time (Fiamma et al. 2007).

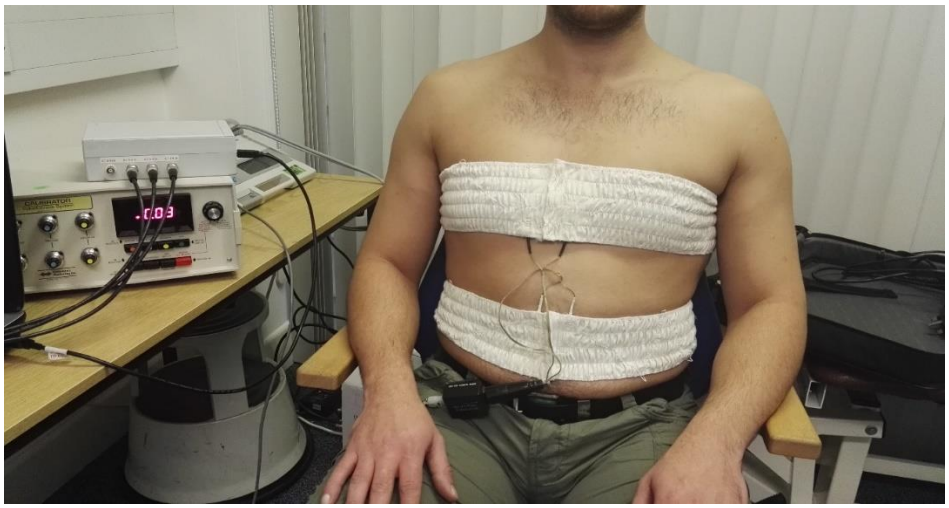


Figure 4-1: Demonstration of allocation of the RIP elastic bands around the ribcage and the abdomen

Measuring absolute air volume components or absolute contributions of the two compartments of the THA to Vt through the RIP requires the application of complex calibration procedures (Konno and Mead 1967; Sackner et al. 1989; Banzett et al. 1995). Uncalibrated RIP signals can be used to estimate timing parameters and amplitudes of the RC and the AB displacement expressed in arbitrary units (Poole et al. 2000). In the literature, several calibration methods have been published over the years to optimise the RIP measurements (Konno and Mead 1969; Sackner et al. 1989). However each calibration procedure has several limitations making this recording method complex, challenging and of limited use in clinical settings. The following sections (4.2.3.1, 4.2.3.2 and 4.2.3.3) provide a brief overview of the RIP calibration procedures.

4.2.3 The theory underlying the calibration procedures

The RIP calibration procedure refers to the determination of a constant of proportionality (K) between the compartmental displacements of the THA and the air volume changes corresponding to each of these regions (RC and AB) during tidal breathing (Konno and Mead 1967). This needs to be determined because different air volume changes occur within each region of the THA due to

anatomical differences. All the calibration procedures are based on the Konno and Mead theory (1967) according to which the Vt can be estimated by the mathematic equation (1) provided in section 4.2.1.

Assuming linearity between the Vt and the changes of the cross-sectional area of each region of the THA, equation (1) has been given as $\Delta Vt = M * [K (\Delta Vt_{RC}) + \Delta Vt_{AB}]$ (2). The ΔVt is the change of air volume inhaled and exhaled at the opening airways; the ΔVt_{RC} and ΔVt_{AB} refer to the change of air volume estimated from the uncalibrated RIP signals of the RC and the AB respectively; the K is a motion coefficient which determines the relationship between the uncalibrated RC and AB signals as derived by each elastic band and the M is a scaling factor for $[K (\Delta Vt_{RC}) + \Delta Vt_{AB}]$ to obtain absolute volumetric parameters. The M can be estimated when the RIP is calibrated compared to the PNT. To estimate relative changes of the Vt, M has been suggested by Konno and Mead (1967) to be set at 1. So the only value, which needs to be computed, is K. In the literature, three different calibration procedures have been widely documented and validated. These are the Isovolume manoeuvre, the Qualitative Diagnostic Calibration (QDC) method and the Fixed-K method.

4.2.3.1 The Isovolume manoeuvre

The Isovolume manoeuvre is the first calibration method applied by Konno and Mead (1967). It requires the individual's cooperation to obtain an optimal value of the motion coefficient K. According to this calibration method, K is estimated when there is fixed volume of air within the THA. With the mouth and nose occluded, individuals are requested to shift as much volume as possible back and forth between the RC and the AB without adding any additional movement through any potential flexion or extension of torso.

This calibration method has been found to be valid offering accurate absolute measures of breathing patterns, such as volumetric indices, compared to the PNT (Barbosa et al. 2012). Nevertheless, it is not considered to be practical, due to requiring active individuals' cooperation. Its use can therefore be of limited in specific group of patients, such as the critically ill patients, too young or old patients and the unco-operative individuals. Thus, Sackner et al. (1989) proposed an alternative retrospective calibration method known as the Quantitative Diagnostic Calibration (QDC).

4.2.3.2 The Qualitative Diagnostic Calibration method

The estimation of K using the QDC method, is derived by the separate calculation of standard deviation (sd) of the uncalibrated RC and AB signals over a period of five minutes of resting breathing prior to the actual recording phase (Sackner et al 1989). The breaths which differ >1 sd

from the sum of the Vt changes within the THA are excluded and K can be estimated by K= - $\frac{sd(\Delta VTAB)}{sd(\Delta VTRC)}$. Considering the RC and the AB as independent units with a single degree of freedom each, this calibration method has the advantage of estimating natural spontaneous variations of regional RC and AB contributions to Vt. This can occur when air volume per breath cycle is believed to be approximately constant within the 5 minute of the calibration period. In the literature, the QDC is the most widely used method, and several studies have examined its accuracy to quantify absolute volumetric indices of breathing patterns (Stromberg et al. 2001; Groote et al. 2001; Barbosa et al. 2012). Stromberg et al. (2001) compared volumetric indices, such as the Vt and the minute ventilation, using the QDC method and the PNT in 10 healthy adults. Measurements were performed in sitting and supine position. Results showed good agreement between the comparable methods in the sitting position, but not in the supine posture. Calibration of RIP was performed only in the sitting position despite obtaining breathing pattern measurements in both the sitting and the supine positions. As additional calibration of RIP was not performed in the supine position, the authors hypothesised that the QDC accuracy could be violated by breathing pattern changes occurring between calibration process and the actual recording condition, due to postural effects.

Groote et al. (2001) highlighted that a critical feature of the QDC method is the assumption of an unknown constant Vt obtained during the five minutes of the calibration process, which can change in different recording conditions. This can therefore affect the optimal estimation of K inducing measurement errors. Moreover, Barbosa et al. (2012) assessed the agreement between the QDC method and the Isovolume manoeuvre in 28 healthy adults in three different positions (sitting, supine and standing). A comparative analysis of K estimation between these calibrations methods showed a lack of concordance for K values among the three positions. The results were theorised to be due to a lack of consistency in individuals' breathing patterns caused spontaneously, or due to postural effects. The authors also suggested that five minutes of resting breathing for calibrating the RIP may not be adequate for individuals with high variability of breathing patterns.

4.2.3.3 The Fixed-K calibration method

To overcome some of the limitations of other calibration methods under differing breathing conditions, the Fixed-K method has been proposed (Banzett et al. 1995). According to this calibration method, K was proposed to stay similar among different breathing conditions with the standard error of Vt being similar over a wide range of K values. Hence, Banzett et al. (1995) stated that the use of a pre-set values of K for different breathing conditions could help to obtain

accurate volumetric indices under different breathing conditions. This could make the RIP's measurements easier, less time-consuming and applicable to several populations.

This calibration method has been validated against measurements derived by a laboratory spirometer in 11 healthy adults of different body types and ages. Based on observational evaluation of individuals' body type and age, fixed values of K were chosen to generate optimal the RC's and AB's signals gain. The authors found that the measurement error for this calibration method was less than 10% when compared to respective Vt measurements obtained by a spirometer during resting breathing. However, firm conclusions about the accuracy of this calibration could not be drawn due to a small sample size with limited availability of a wide range of different body types.

Defining a pre-set of K values for healthy adults may not be an accurately applicable method to quantify breathing patterns of patients who may have increased breathing pattern variability. Poole et al. (2000) stated that the percentage of measurement errors estimated for the fixed-K method was higher compared to the QDC, when infants with respiratory problems and thoracoabdominal asynchrony (TAA) were studied. Based on these findings, the authors concluded that the fixed-K method may not be the preferred calibration method for individuals with dis-coordinated breathing. However, these results are based on a sample of only two infants, raising doubts about the accuracy of fixed-K method until it is tested in larger population and compared to other reference-standard recording methods, such as the PNT.

4.2.4 The validity of the Respiratory Inductive Plethysmography

The measurement accuracy of the RIP has been studied both in healthy adults and patients with obstructive diseases such as COPD, under different breathing conditions (spontaneous breathing, sleep-disordered breathing, and mechanically ventilated patients), at rest or during exercise and in several positions (sitting, lateral and supine position) (Leino et al. 2001; Zhang et al. 2001; Clarenbach et al. 2005; Grossman et al. 2010; Cabiddu et al. 2016). An overview of the evidence regarding the validity of the RIP is summarised in Table 4-1.

Table 4-1: Overview of published validation studies of Respiratory Inductive Plethysmography for measuring breathing pattern components

Study	**Calibration method**	**Breathing parameters**	**Recording posture**	**Breathing condition**	**Participants**	**Comparator method**	**Conclusion**
Leino et al. (2001)	QDC*	Vt*, end expiratory air volume,	Supine	Resting breathing	5 healthy adults 4 patients with lung injury 8 mechanically ventilated patients	PNT*	The RIP was found valid among all examined subjects
Zhang et al. (2001)	QDC	Vt	Supine Lateral	Overnight resting breathing	8 healthy adults 18 patients with apnoea	PNT	The RIP was found to be valid in supine position but not in lateral position
Clarenbach et al. (2005)	QDC	Vt, minute ventilation, RR*, Ti*, Te*, Ttot*	Standing	Breathing during exercise on a treadmill	20 healthy adults 6 patients with COPD 5 patients with heart failure	PNT	RIP was found to be valid for measuring both timing and volumetric indices
Fiamma et al. (2007)	QDC	Vt, RR, Ti, Ttot Vt/Ttot, Vt/Ti, Ti/Ttot Variability of all the above components as determined by CoV%	Supine Sitting	Resting breathing	8 healthy adults	PNT	RIP was found to be valid in sitting and supine posture

Continue Table 4-1

Study	**Calibration method**	**Breathing parameters**	**Recording posture**	**Breathing condition**	**Participants**	**Comparator method**	**Conclusion**
Grossman et al. (2010)	QDC	Vt, minute ventilation, RR	Standing Sitting Lying	Resting breathing during daily life activities	9 healthy adults	Flowmeter	The RIP did not provide valid measurements of volumetric indices in all positions
Hollier et al. (2014)	QDC	Vt, minute ventilation, RR	Sitting	Resting breathing	13 healthy adults 13 obese people (BMI>30kgm^{-2})	Laboratory spirometer	The RIP did not provide valid measurements of volumetric indices in obese people
Cabiddu et al. (2016)	QDC	Vt, RR, minute ventilation	Standing	Resting breathing during constant-intensity exercise	7 healthy male adults	Laboratory Spirometer	The RIP was found valid for measuring RR and minute ventilation at both positions
Retory et al. (2016)	Calibrated with PNT	Vt, RR, Ti, Te	Standing	Resting breathing 6-min walking test	10 obese adults (BMI>30kmg^{-2}) 10 healthy adults (BMI< 25kmg^{-2})	PNT	The RIP was not found to be valid in obese people during both recording conditions

***QDC:** Qualitative Diagnostic Calibration Method; **PNT:** Pneumotachograph; **Vt:** Tidal volume; **RR:** Respiratory rate; **Ti:** Inspiration time; **Te:** expiration time; **Ttot:** Total breathing cycle duration

Leino et al. (2001) examined the measurement accuracy of the RIP for volumetric indices of breathing patterns during resting breathing in supine position compared to the PNT. A paired-sample T-test did not show any significant differences in the examined breathing components between the recording methods. However, due to the reliance of these results only on t-tests, the measurement accuracy of the RIP could not be firmly determined as the identification of any systematic bias could not be observed. Zhang et al. (2001) examined the measurement agreement between the RIP and the PNT for Vt using the Bland and Altman plots (plus estimates of 95% limits of agreement-LOA). In comparison with Leino et al. (2001), breathing patterns were recorded in both supine and lateral position. Zhang et al. (2001) reached the same conclusions as those reported by Leino et al. (2001) in supine position, but measurement agreement between the recording methods was not found in the lateral position. However, this could be due to the lack of an additional calibration of the RIP with QDC method in the lateral position.

While the above studies focused only on validating the air volume components of breathing patterns, Clarenbach et al. (2005) examined the RIP's (via a Lifeshirt with embedded sensors) measurement agreement with PNT for both volumetric and timing parameters during exercise on a treadmill. The authors reported good agreement between the monitoring devices for all examined components during rapid breathing. In contrast, measurement inaccuracies regarding volumetric indices have been reported by Grossman et al. (2010), who examined the use of the RIP to provide continuous measurements of breathing patterns during tasks of everyday life. The breath-by-breath analysis performed in 9 healthy individuals showed that the RIP systematically underestimated Vt and minute ventilation during walking or working on the computer and in different postures, such as standing, sitting and lying position (Grossman et al. 2010). However, proper QDC calibration of the RIP was not feasible under these different recording conditions affecting the accuracy of the RIP. Ambulatory monitoring of breathing patterns using the RIP can be also criticised due to the high probability of introducing noise artifacts in the signals during breathing pattern data acquisition. This, in turn, can have a further impact on the accurate estimation of breathing pattern values when signal processing techniques are applied to extract breathing pattern values. Thus, studies using the RIP for continuous measurements of breathing patterns have been mainly conducted in laboratory settings where ideal recording conditions can be applied.

In addition, the individuals' Body Mass Index (BMI) has been reported to affect the RIP's measurement accuracy (Hollier et al. 2014; Retory et al. 2016). Hollier et al. (2014) examined 13 obese adults (BMI> 30 kgm^{-2}) with coexisting hypoventilation syndrome, and 13 individuals with normal BMI. Breathing patterns were recorded using the Lifeshirt calibrated with the QDC method

and a laboratory spirometer during resting breathing in a sitting position. The Bland and Altman plots showed poor agreement between the recording methods for the RR, Vt and minute ventilation in obese adults but not in healthy BMI adults. The authors also reported that it was not feasible to achieve an optimal fitting of Lifeshirt in some obese people. Similar results were reported in a recent study by Retory et al. (2017) who concluded that large thoracic perimeter and great adipose tissue can be responsible for biasing the RIP's measurements in those with high BMI. Thus, the ability of the RIP to provide valid estimates of quantifiable components of breathing patterns is also likely to be dependent on the correct placement of the bands (Brullmann et al. 2010).

4.2.5 A summary of the Respiratory Inductive Plethysmography as a valid recording instrument

The RIP is a valid monitoring instrument widely used in research. It quantifies compartmental displacements of the THA to estimate a range of quantifiable components of breathing patterns (Clarenbach et al. 2005, Fiamma et al. 2007; Cabiddu et al. 2016). Due to the extensive examination of its validity under different breathing conditions compared to the PNT, it is considered to be a reference-standard monitoring method. It can allow the continuous recording of the natural behaviour of breathing (Fiamma et al. 2007). However, estimation of absolute values of volume-related breathing components requires complex calibration methods, which have been criticised within the literature. Since each proposed calibration method is a complex process, and breathing pattern analysis requires signal processing techniques, its use has been avoided for instant measurements of breathing patterns in clinical practice.

Although estimates of the absolute values of volumetric indices with the RIP can be challenging, this tool can provide accurate estimates of timing parameters via the recording of regional displacements of the RC and the AB irrespective of the application of any calibration method (Wolf and Arnold 2005). However, the accurate estimation of breathing pattern components depends on the quality of data acquisition during the recording process. This depends on the placement of the RIP bands on the individuals' THA and on any body movements apart from those from the THA. This is because measurement errors can be induced, due to the level of artifacts detected in the RIP signals. Monitoring breathing patterns in individuals with high BMI using the RIP, has been also reported to be challenging due to the tight attachment of the RIP bands on increased adipose tissue around the RC and the AB circumferences (Hollier et al. 2014; Retory et al. 2016).

The RIP's measurement principles are based on the assumption of two-degrees of freedom as proposed by Konno and Mead (1967), whose theory is under criticism. According to them, the RC and the AB are considered as independent units of the same coextensive anatomical area with one-degree of freedom in motion each. However, in reality, the AB compartment moves in tandem with the RC compartment and the movement of each compartment of the THA is proportional to the other one, despite their structural differences (Tobin et al. 1983a). In comparison with the Konno and Mead theory (1967), the THA has been suggested to move with more degrees of freedom (Wang et al. 2009). For example, the RC and the AB expand not only anteriorly or posteriorly, but also have vertical and radial movements, which in turn may contribute to respective air volume changes within the whole THA. Other optical-based recording methods have been developed, which do not assume the THA as a two-degree of freedom model.

4.3 Optical-based methods for measuring breathing patterns

4.3.1 The Optoelectronic Plethysmography

The technological development of image processing enabled the development of the optoelectronic motion analysis systems. The Optoelectronic Plethysmography (OEP) was one of the first motion analysis system, which enabled the 3D reconstruction of the THA movements (Aliverti et al. 2000). It is a non-invasive method and uses a series of infrared cameras (2 to 8 cameras) and 87-89 reflective markers attached on specific anatomical reference points of the external surface of the THA (anteriorly, laterally and posteriorly). In comparison to the RIP, the OEP measures the displacement of three compartments of the THA, reported as the pulmonary RC, the abdominal RC and the AB (Aliverti et al. 2001). The pulmonary RC refers to the area between the clavicles and the xiphoid process (see Figure 4-2). The abdominal RC refers to the area between the xiphoid process and the costal margin and the AB refers to the area between the costal margin and the bilateral anterior iliac crest. This technique, theoretically, can provide a better understanding of breathing kinematics where deformities of THA movements can be assessed in more regions of the THA compared to what the RIP quantifies. The OEP has been therefore proposed to enable a breath-by-breath evaluation of the air volume changes within more regions of the THA (Romagnoli et al. 2008).

Operation of the OEP is based on the detection of the movement of reflective markers composed of plastic spheres or hemispheres (six to ten millimetres in diameter) and covered with a reflective paper (Massorini et al. 2017). The markers are allocated on individuals' bare skin by a bi-adhesive hypoallergenic tape creating a grid pattern on individuals' THA. The grid pattern consists of seven horizontal rows between the clavicles and the iliac crest. There are also seven

posterior horizontal rows between the C7 and the posterior axillary lines. The 3D coordinates of each reflective marker are captured by four to eight synchronised digital cameras. These are used to capture the displacement of the reflective markers corresponding to the motion of the THA (Romagnoli et al. 2008).

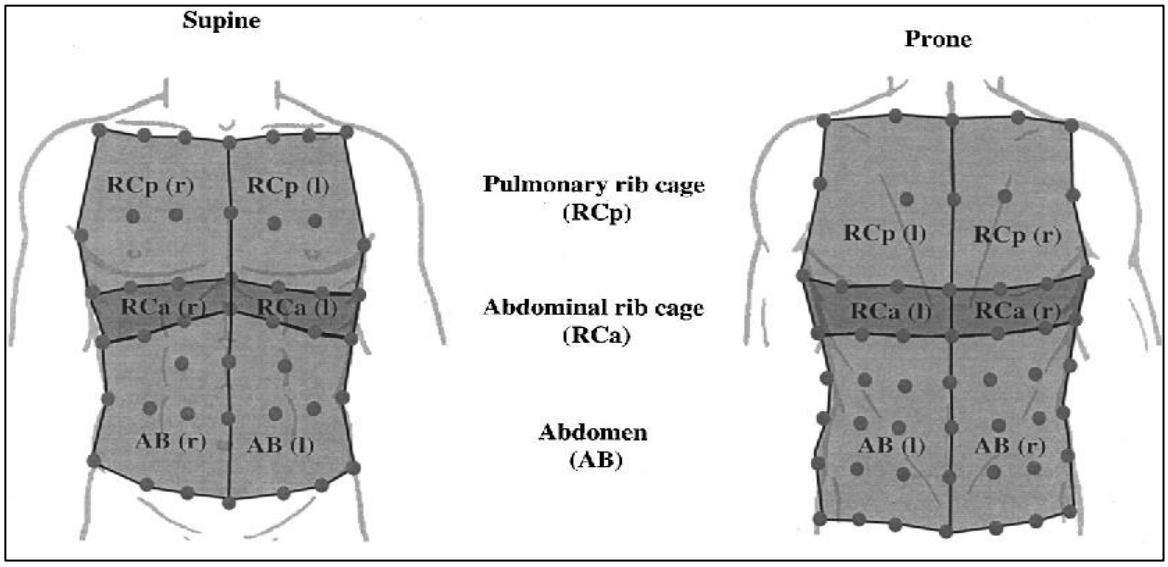


Figure 4-2: Example of allocation of reflective markers on anatomical reference points in accordance with compartmental divisions of thoracoabdominal area

After computing the 2D coordinates of all reflective markers, the system can automatically generate the 3D coordinates of the different reflective markers using stereo-photogrammetry (Layton et al. 2013). The accuracy of the OEP measurements for the air volume components can be influenced by the subsequent processing of acquired data, and the automatic calibration procedures performed within the system (Ferrigno et al. 1990). Two automatic calibration procedures are used to estimate the 3D coordinates. One of them corrects potential optical distortions in the three axes of the geometrical model reconstructed by the system. The other determines the geometric parameters of the collinearity equations used to compute the 3D coordinates.

When the 3D coordinates of each marker are calculated, absolute air volume parameters are estimated through the connection of the points in the reconstructed model within the software, which constitute a net of tetrahedral triangles (Aliverti and Pedotti 2003). The sum of air volume changes in all compartments of the THA is deemed to be equal to the total change of the volume of inhaled and exhaled air at the airway opening (nose or mouth) (Parreira et al. 2012). One of the advantages of the OEP compared to the RIP is that calibration procedures are fast and automatic, without requiring individuals' cooperation or any application of additional calibrations under different breathing conditions (Parreira et al. 2012).

4.3.1.1 The accuracy of the Optoelectronic Plethysmography

A growing number of studies, that have been used the OEP to measure several quantifiable components of breathing patterns in research, have been published. The OEP has been used to record breathing patterns in healthy individuals (Aliverti et al. 2003; Aliverti et al. 2010), or patients with COPD (Bianchi et al. 2004; Vogiatzis et al. 2005; Bianchi et al. 2007), or asthma (Filippelli et al. 2003), at rest (Aliverti et al. 2001; Skoczylas and Sliwinski 2007), during exercise (Romagnoli et al. 2006;Wust et al. 2008; Vieira et al. 2014), and under different postures (Wang et al. 2009; Romei et al 2010). However, concerns have been raised about the OEP's performance when fewer reflective markers and cameras have been used. Use of fewer reflective markers and cameras was proposed to simplify the standard recording approach of the OEP, which requires a large number of markers (n=89) and cameras (n=8) to acquire good quality of breathing pattern data (Layton et al. 2013; Parreira et al. 2012; Massaroni et al. 2017). The Table 4-2 provides an overview of the evidence regarding the use of different recording approaches of the OEP for breathing pattern measurements under different recording conditions compared to the PNT.

Aliverti et al. (2000) initially used 45 reflective markers and 4 cameras to measure volumetric indices of breathing patterns during resting breathing and under supporting pressure ventilation in supine position. The authors stated that the use of this number of markers underestimated measurements of Vt in comparison with the PNT with discrepancies between comparable methods being larger during supporting pressure ventilation. However, the recording period in this study was only 30 seconds, which raises concerns about the representativeness of the breath cycles taken over longer periods. In a later study by the same authors, a longer recording period was used along with the use of improved geometrical and mathematical chest models to improve the OEP's accuracy in supine and prone positions (Aliverti et al. 2001). Good agreement between the OEP and the PNT was found for measuring volumetric indices during resting breathing and deep breathing in supine position, but the authors did not report the exact number of markers used in their study.

Table 4-2: Overview of published validation studies using the Optoelectronic Plethysmography with different recording approaches for breathing pattern measurements in different studied populations and recording conditions

Study	**Recording approach**	**Breathing parameters***	**Posture**	**Breathing condition**	**Population**	**Comparator method**	**Conclusion**
Aliverti et al. (2000)	45 markers 4 cameras	Vt, changes of Vt occurred within Vtrcp, Vtrca and Vtab	Supine	Resting breathing During pressure support at different pressures	11 healthy adults 6 patients with lung injury 7 patients with acute respiratory distress syndrome	PNT*	Poor agreement between devices during volume increases
Aliverti et al. (2001)	Not reported	Vt, changes of Vtrcp, Vtrca and Vtab	Supine Prone	Resting breathing Deep breathing	10 healthy adults	PNT RIP*	Good agreement between the OEP and the PNT. Low agreement between the OEP and the RIP for % contributions to Vt
Duranti et al. 2002	89 markers 4 cameras	Vt, inspiratory capacity (as determined by the difference between TLC and FRC), RR, Ti, Te, Ttot, Ti/Ttot	Sitting	Resting breathing Breathing after inhalation of 200µm albuterol	13 adults with COPD	PNT	Good agreement between the comparable methods for all examined variables during both resting breathing and after bronchodilation

Study	Recording approach	Breathing parameters*	Posture	Breathing condition	Population	Comparator device	Conclusion
Boudarham et al. (2013)	52 markers 6 cameras	Volumetric indices	Supine	Resting breathing	20 patients with different BMI and restrictive respiratory diseases	PNT	Low agreement between the comparable methods for measuring volumetric indices in people with high BMI
Layton et al. (2013)	Not reported	Vt	Sitting	During submaximal and maximal exercise on cycle ergometer	30 healthy adults	PNT	Good agreement between the comparable methods
Nozoe et al. (2014)	66 markers 81 markers 8 cameras	ΔVt, ΔVtrcp, ΔVtrca, ΔVtab	Supine Lateral	Resting breathing	18 healthy adults	PNT	Good agreement between the comparable methods
Vieira et al. (2015)	Not reported	Vt, inspiratory capacity, RR, Ti, Te and Ttot	Sitting	Resting breathing During submaximal exercise	12 healthy adults	PNT	Poor agreement between the comparable methods only for inspiratory capacity during exercise

***PNT:** Pneumotachograph; **RIP:** Respiratory Inductive Plethysmography; **Vt:** Tidal volume; **Vtrcp:** volume of air estimated at pulmonary ribcage; **Vtrca:** volume of air estimated at abdominal ribcage; **Vtab:** volume of air estimated at abdomen; **RR:** respiratory rate; **Ti:** Inspiration time; **Te:** expiration time; **Ttot:** total breathing cycle duration; **ΔVt:** differences in tidal volume; **ΔVtrcp:** differences in volume of air estimated at pulmonary ribcage; **ΔVtrca:** differences in volume of air estimated at abdominal ribcage; **ΔVtab**: differences in air volume estimated at abdomen

In contrast, a recent validation study suggested systematic bias between the OEP and the PNT for volumetric indices in the supine position, when 52 reflective markers were used (Boudarham et al. 2013). Low agreement between the recording methods was assumed to be due to the inclusion of obese adults in this study. As optimal placement of markers in anatomical reference points was not feasible in some obese people (BMI >30kg/m^2), acquisition of valid breathing pattern data was not likely to be achieved. Nevertheless, good measurement accuracy of the OEP for estimating changes of volumetric indices in healthy adults at several positions (supine and lateral) has been confirmed by Nozoe et al. (2014). The latter authors used a larger number of reflective markers (n=66) and 8 cameras in the supine position and 81 markers in the lateral position.

In addition, Leyton et al. 2013 examined the OEP's accuracy for timing parameters and Vt in 30 healthy adults during submaximal and maximal exercise on a cycle ergometer. The number of markers used is not reported, but no significant differences and good agreement between the OEP and the PNT for all examined variables were found in the sitting position. However, the OEP recorded slightly higher values of Vt. Similar results were also documented by Vieira et al. (2015), who examined the ability of the OEP to measure inspiratory capacity. Inspiratory capacity was determined by the difference between total lung capacity and functional residual capacity. To estimate individuals' inspiratory capacity, a specific manoeuvre was performed by the studied individuals both at rest and during submaximal exercise on a cycle ergometer. Results showed good agreement between the OEP and the PNT for all the examined variables (Vt, RR, Ti, Te, Ttot) apart from the inspiratory capacity measured during exercise. This could be attributed to the additional movement of the individuals' torso during the performance of the manoeuvres to measure inspiratory capacity during exercise.

Based on the above reported findings in the literature, the OEP's measurement accuracy for breathing pattern measurements is dependent on the quality of data acquired by the equipment after applying different number of reflective markers and cameras (Parreira et al. 2012). Good quality data requires optimal placement of enough reflective markers of appropriate size on specific reference points of the THA, and the optimal identification of all these markers by enough number of cameras (Romagnoli et al. 2008; Leyton et al. 2013; Massaroni et al. 2014).

4.3.1.2 The shortcomings of the Optoelectronic Plethysmography

The OEP was developed to monitor healthy and altered volumetric indices of breathing patterns at rest and during increased metabolic demands under several breathing conditions, without requiring complex calibration methods in comparison to the RIP (Aliverti and Pedotti 2003;

Romagnoli et al. 2008; Layton et al. 2013; Massaroni et al. 2017). However, the number of markers and their exact allocation on specific reference points of THA is an important factor for the optimal acquisition of breathing pattern data (Romagnoli et al. 2008). Although the use of 89 reflective markers has been standardised in the sitting and standing position (Parreira et al. 2012; Massaroni et al. 2014), the OEP's measurement accuracy can be biased in supine, lateral or prone positions by the need of fewer markers in these positions (Boudarham et al. 2013).

The OEP is generally a laboratory based equipment, and has been used only in research. Its clinical applicability has been of limited use due to its lack of portability and the need for spacious laboratories for its set-up (Massaroni et al. 2017). The precise placement of the markers can be time-consuming and challenging, requiring experience to correctly identify the anatomical locations, combined with a good understanding of the recording process (Layton et al. 2011). Wrong allocation of reflective markers are likely to result in a lack of their identification from the system, requiring their re-adjustments and good quality of data acquisition (Layton et al. 2011). When the OEP was validated in obese adults, the palpation of the reference points was reported to be challenging (Boudarham et al. 2013). Monitoring breathing pattern components via the OEP also requires individuals to be bare-chested. The use of the OEP has been reported in research studies, which mainly involve male individuals. This can be perceived as a not suitable monitoring method for some individuals, especially for female participants in research studies.

4.3.2 The Structured Light Plethysmography

The Structured Light Plethysmography (SLP) is another recently developed monitoring method based on optical measures. In comparison to the OEP, it uses a simpler fully-contactless recording approach to monitor the THA movements (Levai et al. 2012). It was initially designed and developed as a simple technique for assessing lung function in children who were unable to co-operate with Spirometry. (De Boer et al. 2010). During its development, the potential for recording information beyond single maximal breath efforts became apparent and therefore it was developed to measure a range of quantifiable breathing pattern components after a breath-by breath analysis over time.

The SLP is a non-invasive motion analysis system, which uses pc gaming/movie techniques to capture in real time the anterior displacement of the THA. The anterior THA refers to the anatomical area on the front of the chest surface, between the clavicles and the umbilicus (De Boer et al. 2010). In comparison with the OEP and the RIP, the SLP allows the measurement of breathing through the stereoscopic analysis of respiratory-related distortions of a black and white grid pattern (known also as a checkboard). This is projected onto the anterior surface of the THA.

Unlike the OEP or the RIP, the SLP is fully contactless and does not require the allocation of reflective markers on specific reference points of the THA, or the use of two small elasticated bands (see Figure 4-3) (Levai et al. 2012). On the other hand, the SLP only measures the anterior displacement of the THA, and not the whole circumferential movement. As a result, potential lateral and posterior movements of the THA are discounted and this can be perceived as a shortcoming of this recording method.

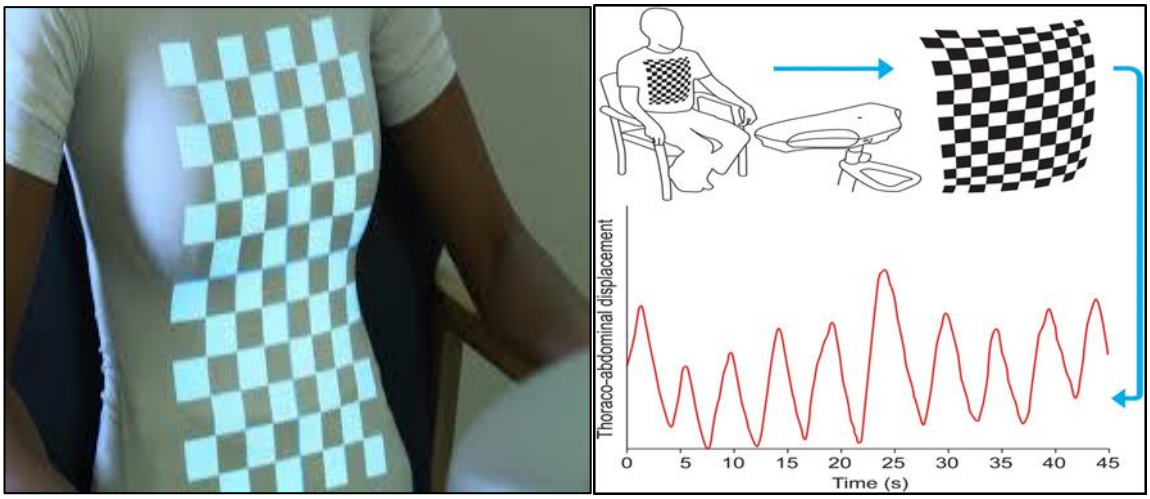


Figure 4-3: Illustration of the checkboard projected by the Structured Light Plethysmography for quantifying thoracoabdominal area movements providing a time-series output (pictures were taken by Motamedi-Fkhr et al. 2017b)

The SLP consists of a projector and two digital cameras set at different angles (De Boer et al. 2010). The grid pattern projected onto the THA consists of a finite number of grid intersections points. An intersection point is defined as the corner that it is shared by four squares consisting of width-grid x height-grid of these points (Levai et al. 2012). Changes in the grid-pattern are captured by the two digital cameras due to the distortion of the intersection points corresponding to the displacement of the THA during breathing (De Boer et al. 2010). The axial displacement of the virtual grid pattern provides a one-dimensional movement trace over time, which is illustrated on a computer screen attached on the device. A dedicated algorithm can be used to provide instant measurements of timing parameters (RR, Ti, Te, Ttot, Ti/tot and Ti/Te) and RC and AB contributions to THA motion (expressed in %) during expiration phase, but not absolute air volume components for which previously discussed monitoring methods were designed (De Boer et al. 2010).

A 3D-reconstruction of the anterior surface of the THA can be provided by the SLP, allowing visual assessment of the motion of the THA and its different compartments in real time. In comparison to the RIP, calibration coefficients obtained experimentally through complex calibration procedures are not required by the SLP. An automatic calibration is provided after the initial

installation of the software of the device (De Boer et al. 2010). Since the SLP was developed to quantify movements of the whole anterior surface of the THA, it is purported that it can provide useful information about breathing kinematics of different regions of the THA which could be missed by using small bands like the RIP uses. Therefore, the SLP can theoretically measure regional contributions to the THA motion not only from the whole RC and AB area but also from the left, the right hemisphere of the thorax, and the quadrants of the THA.

The main advantage of the SLP is its fully contactless nature, as there is no need for using any physical attachment between the individuals and the equipment. Another advantage is its portability due to its compact size, and its ability to provide instant measures of quantifiable components of breathing patterns. Breathing pattern data analysis via the installed software does not require retrospective signal processing techniques for breathing pattern data extraction. These features have been reported to contribute to the feasibility of collecting breathing pattern data in different clinical settings (Elshafie et al. 2016; Motamedi-Fkhr et al. 2017a).

The simple projection of the grid-pattern on individuals' chest wall while seating or laying down makes it less likely that individuals would modify of breathing patterns in response to the measurement, because they may have limited awareness of the recording process (Levai et al. 2012). This may further facilitate a better measurement of individuals' natural behaviour of breathing, without inducing instrumental changes. Han et al. (1997) examined whether the awareness of breathing measurements could interfere with the individuals' tidal breathing at rest. Data from 74 healthy adults were collected using the RIP, when there was individuals' misperception of being recorded and when they were aware of being recorded. Authors found that when people knew that their breathing was recorded, they tended to prolong both inspiration and expiration phase, decreasing the RR.

A recent study by Nierat et al. (2017) examined the ability of the SLP to reduce instrumental observer effect on breathing pattern measurements by comparing individual SLP measurements with simultaneous measurements of the SLP and the PNT. Analysis of the variability of quantifiable components of breathing pattern collected from 30 healthy adults and 30 adult patients with COPD showed significant differences between the use of SLP in isolation and the simultaneous use of the SLP and the PNT in both groups (Nierat et al. 2017). Thus, the authors concluded that measuring breathing via the SLP could allow the recording of the natural variability of breathing patterns over time.

4.3.2.1 The accuracy of the Structured Light Plethysmography

Despite the theoretical advantages of SLP to record quantifiable breathing pattern components of interest for this research presented in this thesis, a limited body of evidence has examined its accuracy. To date, although the SLP has been used to monitor differences in breathing patterns between healthy children and those with asthma before and after bronchodilator (Hameidi et al. 2017), its accuracy to measure quantifiable components of breathing patterns under different recording conditions, in comparison to other non-invasive recording methods, has not been examined. At the time of conducting the independent SLP validation study between 2015 and 2016 reported in this thesis, only conference abstracts reporting the correlation of SLP measurements with a laboratory spirometer for timing parameters, had been published (Iles et al. 2015; Ghezzi et al. 2015). At the time of writing this thesis, there was still a limited body of published evidence examining the properties of this relatively new monitoring method.

The ability of the SLP to record differences in breathing patterns among patients with lung resection in a clinical setting and between healthy adults and those with COPD was examined by Elshafie et al. (2016) and Motamedi-Fakhr et al. (2017a) respectively. The feasibility of using the SLP in clinical settings was supported in both studies. Elshafie et al. (2016) recorded regional %RC and %AB contributions to THA movements the day before and one day after the surgery in 15 patients with lung resection. The post-operative SLP measurements showed a significant reduction in the relative contribution of the operated part of the thorax compared to the pre-operative SLP measurements supporting the ability of SLP to detect changes in THA movements. Motamedi-Fkhr et al. (2017a) reported that the SLP was additionally able to detect differences in timing components (RR, Ti, Te, Ti/Ttot) between healthy adults and patients with COPD. The authors highlighted the potential use of the SLP as a monitoring method to facilitate assessments of quantifiable breathing pattern components in clinical practice. Although both studies suggest that the SLP measurements show some responsiveness to change in response to an intervention (surgery) or pathology, these changes were not compared to other current reference standard monitoring methods for estimating any systematic bias generated by the SLP.

A more recent study by the same authors examined the measurement agreement between the SLP and the PNT for timing components (RR, Ti, Te, Ttot, Ti/Te and Ti/Ttot), in both healthy and patients with different obstructive diseases, including asthma (Motamedi-Fakhr et al. 2017b). The authors found good agreement between the comparable methods for all timing components during resting breathing irrespective of the diversity of breathing patterns from the different studied populations. The measurement agreement was examined within a fairly short-period (45 seconds), which is likely to provide only 6-8 breath cycles. However, to date, the available

evidence related to the SLP's validity comes from research that has been mainly conducted by the manufactures of this monitoring method. It was therefore deemed necessary to conduct an independent validation study prior to determining if the SLP was an appropriate tool for this research. The study would help to understand the SLP's performance under different recording conditions for longer periods of time, compared to a current non-invasive reference standard monitoring method, such as the Respiratory Inductive Plethysmography.

4.3.3 Summary of the chapter: The rationale of conducting the validation study

In clinical practice, monitoring breathing patterns can be challenging potentially due to the lack of a clinically objective monitoring method, which does not require complex calibration procedures and a time-consuming set-up process within spacious laboratories. Several non-invasive technologies have been identified to provide accurate estimates of several breathing pattern components, but they are mainly used for research purposes. The RIP and the OEP are the most extensively studied methods in the literature and their accuracy has been examined under various recording conditions in different populations supporting their validity.

On the other hand, the SLP has been recently developed to monitor timing parameters and the THA movements with the potential of being used in clinical practice, due to its simple set-up, portability and ability to provide instant measurements of breathing patterns. This, in theory, may enable the use of this device by most health professionals. However, it is clear that there is need for more independent research regarding the SLP's accuracy under different recording conditions compared to reference standard non-invasive methods. Although the SLP is already being sold commercially for clinical use as a simpler recording method compared to the RIP and the OEP, it was deemed necessary by the researcher to further examine its performance prior to making a decision about which recording device to be used in this research. This new recording method was believed by the researcher to be useful due to the advantages derived by its novelty of using a contactless recording approach. This in theory may make it less likely to interfere with breathing and allows the recording of natural behaviour of breathing over time.

To conduct a validation study to examine the criterion-validity of the SLP, a comparator method had to be chosen. The RIP was selected as a comparator recording method. This was because it is a commonly recognised reference standard technology, which quantifies compartmental displacements of the THA to estimate averaged and breath-by-breath estimates of breathing patterns over time (Clarenbach et al. 2005, Fiamma et al. 2007). In addition, it was feasible to obtain simultaneous measurements from both devices under different recording conditions. Although the OEP is recognised as another valid recording method with similar measurement

principles to those used by the SLP, it was not feasible to be used as a comparator device in the validation study. This was because of the potential interference between the SLP and the OEP recording methods according to their manufacturers' guidelines.

Recording breathing patterns with the SLP requires individuals to be fitted in a white t-shirt for the accurate projection of the grid pattern on their THA. The reflective markers used by the OEP would therefore have to be placed on the outside of the T-shirt to be visible from the cameras used by the OEP. This could cause data acquisition problems between the projection of the SLP's grid pattern and the identification of reflective markers by the cameras of OEP. In addition, any attachment or the presence of wrinkles on the clothing used by the SLP is likely to induce artifacts in the signal obtained by the SLP (Layton et al. 2013). The use of the OEP as a comparator was therefore discounted. The RIP was usable as a comparator because its two elastic bands could be placed underneath the close-fitting white t-shirt required by the SLP, without affecting data acquisition. In the next chapter of this thesis, the validation study of the SLP is presented.

Chapter 5 The validation study of the Structured Light Plethysmography

In this chapter, the validation study is presented and the findings of the study are discussed. A limited body of evidence has examined the SLP's performance under different recording conditions compared to non-invasive recording technologies, such as the Respiratory Inductive Plethysmography (RIP). As a result, this study was conducted to further examine the SLP's criterion validity and its responsiveness for breathing pattern measurements as another form of technology prior to determining the potential use of quantifiable breathing pattern components as a physiological marker in asthma management.

5.1 Aims of the validation study

The primary aim of this study was to examine the criterion validity of the SLP compared to the RIP at rest and immediately after exercise. The nature of the SLP recording procedure makes recording during exercise impossible. The examined quantifiable breathing pattern components were: a) timing parameters and b) parameters associated with the THA movements during both inspiration and expiration phase. A list of the examined breathing pattern components and a definition of each is provided in section 5.2.6. This validation study was also aimed to examine the SLP's accuracy under rapid breathing rather than resting breathing. Exercise was used as a means to increase the individuals' metabolic demands, resulting in an increase in the RR. The ability of the SLP to agree with the RIP about any changes in the examined breathing pattern components induced by exercise was secondary examined.

5.1.1 Hypothesis and objectives

The hypotheses of this validation study were

1) The SLP can provide accurate estimates of quantifiable breathing pattern components (such as timing parameters and a parameter associated with the proportionality of RC motion to AB motion (RC/AB) during both respiratory phases under different breathing conditions
2) The SLP is comparable to the RIP for identifying any changes in the above breathing pattern components between resting breathing and after submaximal exercise.

Based on the above, the objectives of this study were:

1) To collect breathing pattern data at rest and immediately after submaximal exercise on a cycle ergometer using the SLP and the RIP at the same time.

2) To examine the averaged measurement agreement of the RIP and the SLP for the examined breathing pattern components at rest and after exercise.

3) To evaluate a breath-by-breath agreement between the comparable methods for the examined breathing pattern components. Performing a breath-by-breath analysis helped to obtain a variety of magnitudes of examined breathing pattern components through which the maintenance of agreement between comparable recording methods could be checked. This could also help to observe any violation of the measurement agreement between the recording methods due to any within-individual variability of breathing pattern components over time.

4) To assess the measurement agreement between the monitoring methods for any change in the examined breathing components after exercise.

5.2 Methods of the validation study

5.2.1 Study design

An observational cross-sectional study design was used to obtain breathing pattern data simultaneously from the SLP and the RIP at the same time a) at rest and b) immediately after submaximal exercise. This study design was used to meet the aims of this validation study and answer the research question: is the SLP a valid and responsive monitoring method for breathing pattern measurements under different breathing conditions compared to the RIP? Breathing pattern components were therefore recorded twice (5-minute recording at rest and 5-minute recording immediately after submaximal exercise) in a sitting position using the SLP and the RIP within a single data collection session. The total duration of each session ranged from 30 to 40 minutes.

5.2.2 Setting and ethical considerations

Prior to the participants' recruitment and data collection, the study had been peer-reviewed and ethically approved (Ethic number: 18396) from the School of Health Sciences, Faculty of Environmental and Life Sciences, University of Southampton on the 3rd February 2016 (see Appendix B). Willing adults who met the inclusion criteria were invited to attend a single recording session at the research laboratory 0003, Building 45, Highfield campus, University of Southampton.

5.2.3 Participant's eligibility

Volunteer individuals aged 18 or over with varying BMI who were able to provide informed consent were eligible to take part in the study. Individuals with any obvious acute respiratory symptoms (such as sneezing, coughing) on the day of data collection were excluded, since this could interfere with the quality of data acquisition from both devices. Good quality of data acquisition requires minimal noise artifacts to be included in the sum output of time series generated by comparable methods; analysis of which was beyond the scope of this validation study.

Individuals were also not eligible to take part in the study if they could not complete a 10-minute incremental exercise protocol on a cycle ergometer, due to any acute musculoskeletal pain or a self-reported cardiovascular problem. The eligibility criteria permitted both healthy adults and adults self-reporting history of a respiratory problem, such as asthma, to take part in the study. This was because the primary interest of this study was to assess the measurement accuracy of the SLP in comparison to the RIP, irrespective of the underlying breathing patterns of studied individuals. In the event, 4 individuals with self-report history of asthma (no use of medication during the past 5 years) were recruited. However, their lung function tests did not reveal any fixed airway obstruction or decline of airflow limitation. Consequently, their breathing pattern data were analysed along with those derived from healthy individuals characterised by normal lung function measurements.

5.2.4 Participants' recruitment

After gaining permission from different Faculties within the University of Southampton, posters (see Appendix B) were displayed on notice boards to enable the participants' recruitment. The posters were also distributed to students who were attending lectures in the School of Health Sciences, Building 45, Highfield campus. Upon contact, the researcher checked whether individuals were eligible for the study using a screening sheet (see Appendix B). Then a participant information sheet (see Appendix B) was given to those who were eligible and willing to take part in the study. The recruitment process and the data collection procedure took place between February 2016 and April 2016.

5.2.5 Sample size

Calculation of an adequate sample size for a method comparison study has been suggested to be dependent on the level of accuracy for the estimates of limits of agreement between the comparable methods (Bland and Altman 1986). When the level of accuracy of the limits of

agreement for an examined variable is known, a sample size can be calculated via mathematical equations proposed by Bland and Altman (1986). This equation is based on the estimation of the expected width of confidence intervals for both upper and lower limit of agreement using values of standard deviation (sd) of the expected optimal difference between the comparable methods for an examined variable. For this study, there were no well-defined normative ranges of differences between current monitoring methods for the examined breathing pattern components. The sample size of this study was therefore based on a pragmatic choice, and was comparable to sample sizes used in previous validation studies of the RIP in the literature (Clarenbach et al. 2005). Thus, a convenience sample size of 50 individuals was chosen.

5.2.6 The examined breathing pattern components

The examined breathing pattern components were a) timing parameters and b) parameters associated with the THA movements.

Timing parameters involved were:

- The inspiration time (Ti); It was measured in seconds and defined as the time during which air is actively inhaled in the lungs as a result of the THA expansion during the inspiration phase. It was calculated as the time between the lowest point of a trough and the next peak on the respiratory waveform of the sum output signal from both the RIP and the SLP.
- The expiration time (Te); It was measured in seconds and defined as the time when air leaves the lungs as a result of either relaxation of the THA (at rest) or potential active expulsion (after exercise) during the expiration phase. It was calculated as the time between a peak (start of expiration phase) and the next lowest point of a trough on the respiratory waveform of the sum output signal from both the RIP and the SLP.
- The total breath cycle duration (Ttot); It was measured in seconds and defined as the sum of the Ti and the Te representing the time needed to complete a whole breath cycle including any pause at the end of either inspiration or expiration phase.
- The ratio of the Ti/Te represented a measurement of proportionality between both respiratory phases.
- The ratio of Ti/Ttot was defined as a measurement of proportionality of inspiration time to total breath cycle duration.
- The Respiratory Rate (RR); It was expressed in number of breath cycles per minute (bpm) and was defined as the number of complete breath cycles in one minute. It was calculated by dividing the total number of complete breath cycles by the number of minutes of the total recording time.

The parameters associated with the THA movements were:

- The inspiratory ribcage amplitude (RC_{ampins}) expressed in arbitrary units. It was defined as the vertical distance between a trough and the next peak on the respiratory waveform obtained by ribcage signals of the RIP ($RC_{ampiRIP}$) and the SLP ($RC_{ampiSLP}$) measuring the displacement of the RC area during inspiration phase. The $RC_{ampiRIP}$ was generated by the circumferential displacement of the RC area on the height of 4^{th}-6^{th} ribs. The $RC_{ampiSLP}$ was estimated by the displacement of the anterior region between the height of clavicles and the end of the xiphoid process. A similar definition was given for the expiratory ribcage amplitude (RC_{ampexp}), expressed in arbitrary units. It was defined as the vertical distance between a peak and the next trough on the respiratory waveform obtained during the expiration phase by RC signals of the RIP ($RC_{ampeRIP}$) and the SLP ($RC_{ampeSLP}$).
- The inspiratory abdominal amplitude (AB_{ampins}) expressed in arbitrary units. It was defined as the vertical distance between a trough and the next peak on the respiratory waveform obtained by the AB signals of the RIP ($AB_{ampiRIP}$) and the SLP ($AB_{ampiSLP}$) measuring displacement of abdomen during inspiration phase. The $AB_{ampiRIP}$ was generated by the motion of circumferential area at the height of umbilicus. The SLP's abdominal signal ($AB_{ampiSLP}$) was produced by the displacement of the anterior region between the end of the xiphoid process and the height of umbilicus. A similar definition was given for the expiratory abdominal amplitude (AB_{ampexp}), expressed also in arbitrary units.

In previous studies where the RIP had been calibrated, the weighted sum of either RC_{ampins} and AB_{ampins} or RC_{ampexp} and AB_{ampexp} was taken as representing relative breath volume (measurements of the Vt) during inspiration and expiration phases respectively (Hollier et al. 2014). There is currently no information regarding a weighting factor that might give an equivalent calibration for the SLP and thus the relation of the motion to volume is unknown for the SLP. Therefore, no attempt was made to combine the measurements of the AB_{amp} and the RC_{amp} in either device, but direct comparisons between the RC_{ampRIP} and the RC_{ampSLP}, and between the AB_{ampRIP} and the AB_{ampSLP} during both respiratory phases were made.

Additionally, previous RIP studies have reported the relative contribution of RC_{amp} and AB_{amp} to total chest wall movement expressed as a percentage of the magnitude of RC_{amp} (or AB_{amp}) during respiratory phases (Clarenbach et al. 2005, Fiamma et al. 2007). Although the researcher was interested in the estimation of the relative motion of different regions of the chest wall (such as the RC and the AB) during each breath cycle, the absence of a validated weighting factor for calibrating the SLP made it inappropriate to measure percentage of regional contributions to total THA movement. Instead, direct comparisons of the ratio of the amplitudes of the movements of

the THA (RC_{ampl}/AB_{ampl}) during both respiratory phases were sought to check the agreement between the comparable methods for the proportionality of compartmental displacements of the THA.

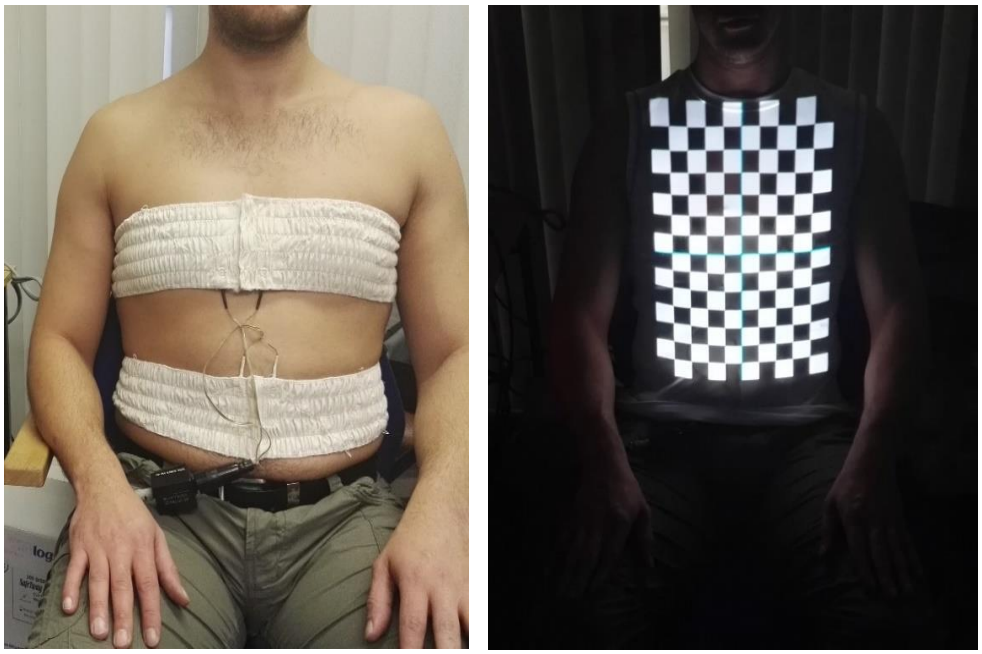
5.2.7 The equipment used in the validation study

Breathing pattern components were recorded simultaneously using both the RIP and the SLP at rest and immediately after exercise, with participants in the sitting position on a straight high-back chair with arms. An Inductotrace system (Ambulatory Monitoring Inc) was used to obtain the RIP breathing pattern data. Electrical gains from the RIP were obtained through two insulated sinusoid wire coils within two wide elastic bands (Inductobands) placed around the individuals' RC at the height of the axillae (armpits) and around the AB circumference at the height of the umbilicus (see Figure 5-1). Changes of the cross-sectional area of the THA circumference at each of these locations were measured in voltage changes over time caused by the expansion and the contraction of the two RIP bands corresponding to THA movements. The obtained RIP signals were transferred to a personal laptop via a data acquisition box, using a sample frequency of 30HZ, which was equal to the fixed-sampling frequency of the SLP. A custom-built analogue-to-digital (A-D) converter was also used to convert the RIP signals into a digital form on the researcher's laptop computer, where saved and used for further analysis in the Matlab software (provided in section 5.2.10).

Breathing pattern data were also collected by the SLP (Thora-3Di^{TM}; Pneumacare Ltd, Cambridge, UK). The SLP is a motion analysis system which uses the projection of a structured grid pattern of light onto individuals' THA. The SLP signal was generated by the distortion of the grid pattern intersection points relating to the displacement of the anterior surface of the THA during breathing as recorded by two digital cameras attached on its head scan. Three different grid sizes were used: 14x10 squares, 12x8 squares and 10x6 squares according to each participant's chest wall diameter (as estimated by tape measures) covering the anatomical area between the height of clavicles and the height of umbilicus as suggested by De Boer et al. (2010). Each participant, according to their body size, wore a close fitting white T-shirt (available in all sizes). Wearing a tight white T-shirt enables the good projection of the SLP's grid pattern on individuals' chest wall and is recommended for good quality data acquisition (Motamedi-Fkhr et al. 2017b) (see Figure 5-1).

The white T-shirt was worn over the RIP bands to allow the simultaneous recordings of breathing pattern components from each device, without the comparable monitoring technologies interfering with each other. The SLP cameras were located in front of each participant (4 feet

away), and the centre of a blue cross within the SLP grid pattern was aligned on each participant's THA. This was performed by asking participants to point the V-shaped notch at the end of xiphoid process with their finger. This was in accordance with the manufacturers' guidelines for optimal breathing pattern recordings using the SLP. The obtained SLP digital time trace was illustrated on a computer screen attached on the device. Once breathing pattern data were collected by the SLP, raw data were exported into CSV files and transferred to the same laptop with the uncalibrated RIP data for further extraction and analysis using the Matlab software (provided in section 5.2.10). Although the SLP software is able to analyse the data automatically, no information about the algorithms used by the SLP equipment was available.



(a) (b)

Figure 5-1: Quantifying breathing pattern components at sitting position in the validation study: (a) recording approach used by the Respiratory Inductive Plethysmography and (b) recording approach used by the Structured Light Plethysmography

5.2.7.1 Other tools used in the validation study

A demographic data sheet was used to collect data relating to the individuals' age, gender, weight and height (see Appendix B). These data were collected to summarise and characterise the sample of the study. Lung function measurements were performed via a portable spirometer (Vitalograph, Alpha) to assess the participants' lung function. The spirometer was also calibrated every time before data collection using a 3-L syringe as recommended by its calibration guidelines. Spirometry measurements were in accordance with the guidelines for implementing optimal spirometry suggested by Miller et al (2005). The participants performed a forced vital capacity manoeuvre for three times and the best values of FEV_1, FVC, and FEV_1/FVC were used.

A cycle ergometer (Corival V_2, Lode Br) was used to allow the individuals to undertake incremental exercise and increase their RR. The height of the saddle and the handlebar could be adjusted to the desired height according to the participants' body size. All the parameters of the exercise protocol were in accordance with the guidelines of ATS/ACCP for exercise testing (ATS/ACCP 2003). The duration of exercise was 10 minutes, including a 3 minute warming up period during which intensity of exercise (resistance to pedalling) was set at 30 Watt. The pedalling frequency was set at 80-90 rpm and the individuals were verbally encouraged to maintain the same pedalling frequency throughout the whole exercise protocol. After 3 minutes, the intensity of exercise was increased by 25 Watt every two minutes until the end of exercise protocol (10^{th} minute). The Borg Scale of Perceived exertion for exercise and dyspnoea was also used to titrate the intensity of exercise on the cycle ergometer as perceived by the participants according to their physical limits (Borg and Kaijser 2006). Numbers from 0 to 10 were presented on the scale of perceived exertion for exercise and breathlessness. This was used to pace individual's submaximal effort during the exercise. This also helped them to maintain a moderate to severe level of exertion, as participants were advised to keep a level of exertion for exercise and dyspnoea at 6 points on the scale.

5.2.8 Data collection procedure

The following flow chart summarises the stages undertaken for each participant during the data collection procedure. Upon arrival and after given informed consent, a demographic data sheet was completed by the researcher (see Appendix B). Lung function test was performed three times for each participant in the sitting position. The participants inhaled as deeply as possible before blowing hard and fast into the spirometer for 6 seconds. Then, participants were fitted with the appropriate size of the RIP bands whilst sitting on high straight back chair with supported arms.

The participants were also requested to wear a white T-shirt on the top of the RIP bands to enable the right projection of the SLP grid pattern. The researcher positioned the SLP in front of the participants and he aligned the SLP grid pattern onto participants' THA as previously described. Breathing patterns were recorded during spontaneous breathing at rest for 5 minutes. During that period, the individuals had been asked to stay still and quiet (no speaking). Remaining still and quiet was necessary to collect good quality of data from both devices avoiding the presence of noise artifacts and baseline shifts on the received signals caused by other body movements. To ensure that the two signals from the RIP and the SLP were synchronised and to avoid potential time delays between the devices, participants were also requested to take a deep breath in and hold it for 5 seconds at the start of each recording period either at rest or after exercise. This manoeuvre could be detected within the signals from each device. After 5 minutes of breathing

pattern recording at rest, individuals were asked to perform 10 minutes of submaximal exercise on the cycle ergometer. The RIP bands and the white T-shirt remained on each participant during exercise. After the exercise phase, participants were immediately recorded for another 5 minutes using the same procedure as before.

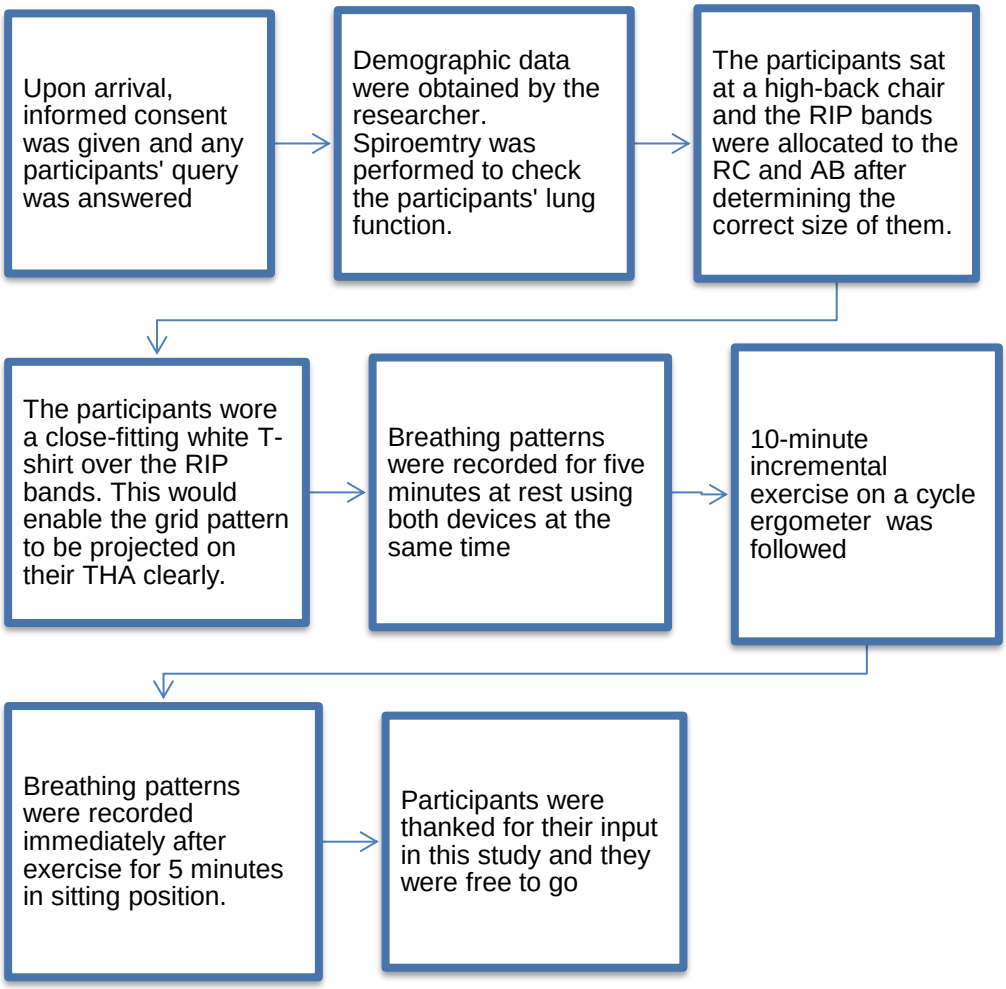


Figure 5-2: Overview of the sequence of events during data collection procedure

5.2.9 Appraisal of data acquisition during the recording session

All the measurements obtained by the RIP and the SLP for each recording period were visually assessed for quality during the recording procedure. This was to ensure that received signals from comparable methods could be used for further data extraction and analysis in the Matlab software. When the RIP or SLP sum output time series traces were deemed to be of low quality, they were discarded. Data were deemed to be of low quality when there were signal baseline shifts or extreme noise artifacts. In the SLP trace, these were illustrated automatically by an orange colour on the SLP respiratory waveform on the computer screen instead of having a continuous blue trace. In the RIP time-trace, these could be observed by the absence of a continuous smooth sinusoidal waveform. When data quality was poor, the recording process was

repeated until good quality of signals was achieved with permission from the participants. The artifacts could be caused by extreme body movements, ill fitting of the RIP bands or presence of wrinkles on the white T-shirt at any time during the recording procedure. Repeating recordings of breathing patterns was performed only in 4 participants at rest with the second attempt to be successful. This was because of some participants' random body movements and their negligence to stay quiet during the recording time.

5.2.10 Extraction of breathing pattern data in the Matlab software

Parameterised data (average values plus standard deviations-sd) of each examined breathing pattern component were extracted using the Matlab software. Each paired raw data sets obtained by the RIP and the SLP was stored in a Matlab.mat file using an individual code for each measurement pair. An algorithm previously written by the researcher's supervisor (Prof Anna Barney) for the research team was used for data extraction (Tehrany 2015). The sum output time series trace of each device was used to extract values of timing parameters, while values of the RC_{amp} and the AB_{amp} were extracted using the individual signals generated by the RC and the AB motion detected by each device.

Although the RIP sum output signal was manually synchronised with the SLP sum output signal during the data acquisition, a second alignment of both signals was performed prior to data extraction to ensure good signal alignment. This allowed the provision of a same length matched sum output signals for data extraction. Since the morphology of the two sum output signals was similar, the tip of the first peak of a breath cycle on the RIP sum output signal after the participants' breath hold was manually selected. The

Figure 5-3 shows an example of the selection of the peak in the first breath cycle identified on the RIP signal after a participant's breath hold.

The same procedure was followed to select the respective tip of the first peak of a breath cycle after the participants' breath hold manoeuvre on the SLP output sum signal. This corresponded to the previously selected peak on the RIP signal. A plot of an aligned and length matched pair of the RIP and SLP traces ready to be used for data extraction is provided in Figure 5-4. The alignment process for each data set was performed three times and visual assessment was performed in each attempt to ensure consistency of the aligned RIP and SLP traces.

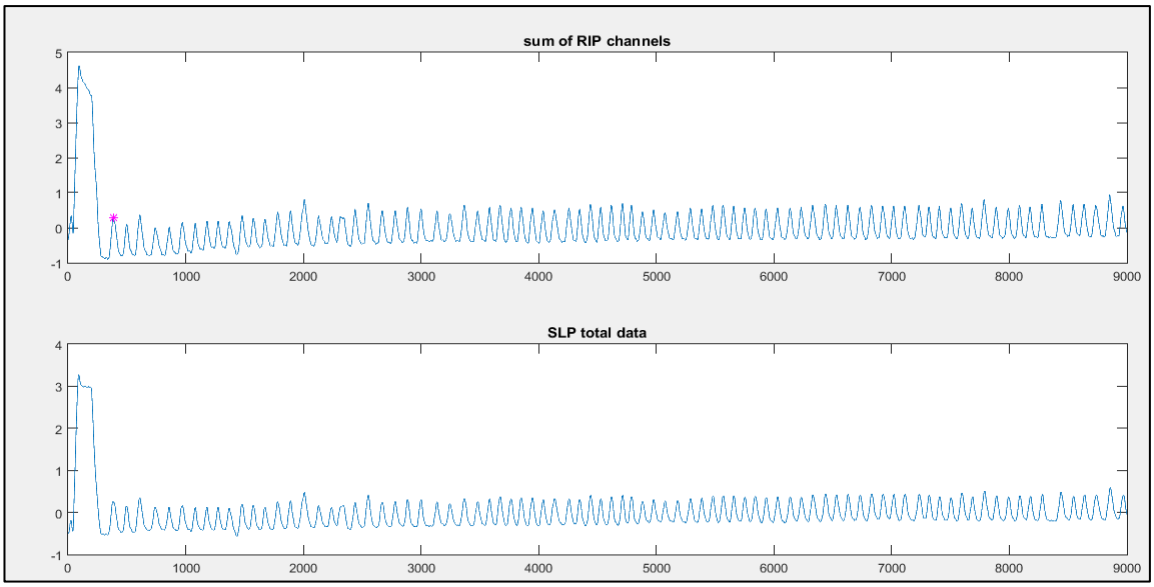


Figure 5-3: An example of the alignment of the received sum output time series traces in the Matlab window with the pink asterisk showing the identification of the first peak of a breath cycle in the Respiratory Inductive Plethysmography signal after a 5-second breath hold

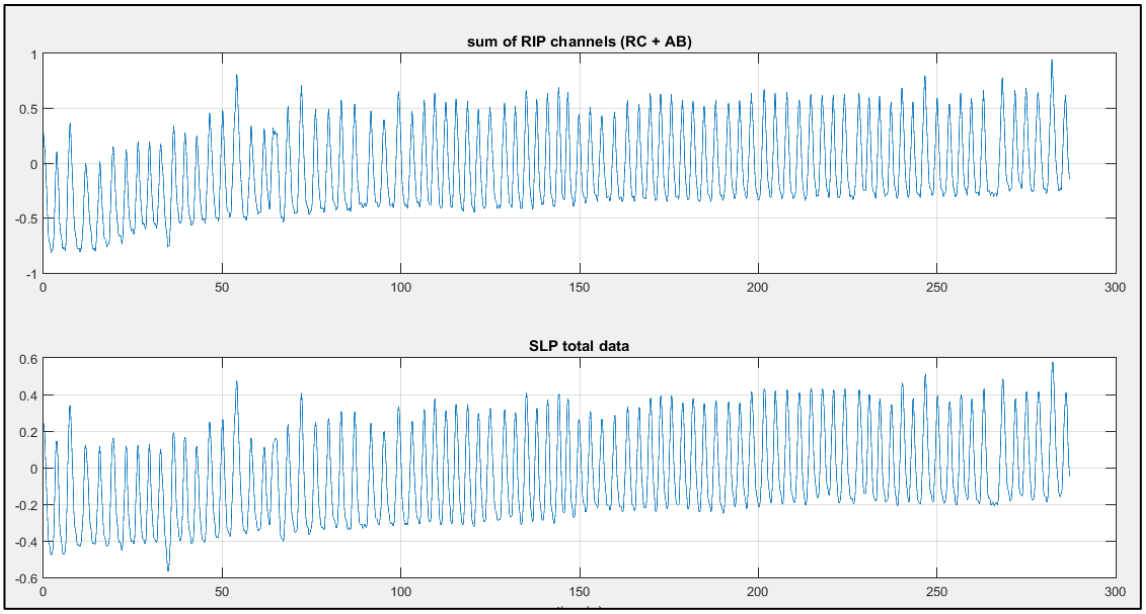


Figure 5-4: An example of an aligned and length matched pair of sum output time series traces received by the Respiratory Inductive Plethysmography and the Structured Light Plethysmography

Once the alignment process of the RIP and SLP signals for each paired measurement was successfully performed, an automatic peak detection algorithm was used to identify local minima and maxima for each inspiration phase of each detected breath cycle throughout the recording period (see Figure 5-5). The RIP sum output signal was firstly processed. The inspiration phases were represented with red colour. Black and red vertical dashed lines were used to denote the beginning and the end of an inspiration phase of each detected breath cycle over the recording time. A trough represented the start of the inspiration time denoting the inspiratory start time of a breath cycle. A peak illustrated the end of inspiration phase and the start of the expiration phase, marking also the start of the expiratory time of each given breath cycle. Despite the use of an automatic peak detection algorithm, the researcher could further edit the signals by removing troughs and peaks in case of not-real breath cycles. This was when consecutive peaks or troughs could be erroneously detected by the automatic algorithm due to presence of noise artefacts or baseline shifts in the aligned sum output traces. During data extraction, all the pairs of the RIP and SLP signals were found to have the same number of breath cycles during each recording period either at rest or after exercise, without the need to remove any not-real breath cycle.

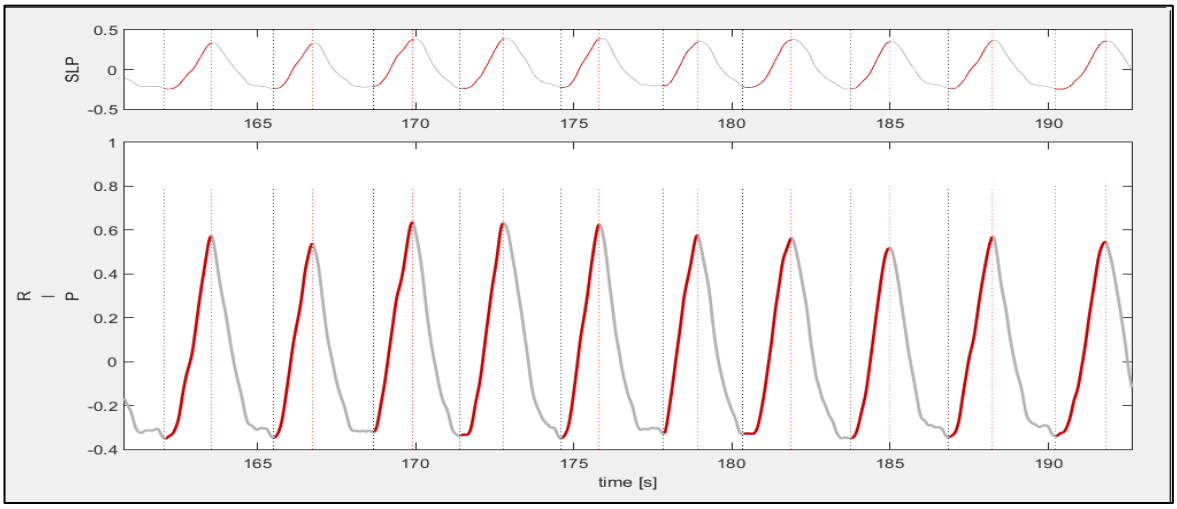


Figure 5-5: An example of detecting local minima and maxima in a zoomed RIP sum output signal marking inspiration phase in given breath cycles with the top of the figure showing respective troughs and peaks on the SLP sum output trace

After using the automatic peak detection algorithm, the values of parameterised data of the examined parameters were provided in the Matlab command window. The breath-by-breath values of the examined breathing pattern components were provided in excel files.

5.2.11 Statistical analysis

At the time of analysing the data of this study, the latest available version of SPSS (IBM statistics 22) was used to perform a statistical analysis. The demographic data (age, gender, BMI) and the lung function measurements were summarised using descriptive statistics to characterise the sample of the study. Parameterised data of the examined breathing components as recorded at rest and after exercise were inserted into SPSS as continuous variables. Mean values (plus sd and 95% confidence intervals- CI) of the examined breathing components were estimated at rest and after exercise. Descriptive statistics were also used to summarise mean values (plus breath-by-breath values) of the differences in the examined breathing components between the RIP and the SLP at rest and after exercise.

Different statistical analyses were performed to check agreement between comparable methods. These involved:

a) The separate examination of averaged agreement between the RIP and the SLP at rest and after the exercise.

b) The breath-by-breath agreement between the RIP and the SLP for all examined breathing components using all measurements from before to after exercise.

c) The examination of the measurement agreement between the RIP and the SLP for the changes in the examined breathing parameters after exercise.

5.2.11.1 The examination of the agreement between the comparable methods

The measurement agreement between two comparable methods refers to the identification of any systematic measurement error (known also as a systematic bias) between the comparable methods (Hernaez 2015). Although the Interclass Correlation Coefficient or the use of linear regression have both been proposed as some statistical approaches to evaluate the strength of linear associations between paired continuous measurements, these approaches have been criticised to evaluate agreement (Bland and Altman 2010). This is because they are not likely to quantify any systematic bias between two comparable methods, nor do they provide limits of agreement (LOA) between the comparable methods.

The Bland and Altman plot providing the 95% LOA is a graphical approach used not only to visually examine the agreement between comparable methods but also to quantify any systematic bias (mean difference) between the comparable methods (Bland and Altman 1999). In the Bland and Altman plot, the differences in a quantifiable variable between the comparable methods are plotted in the y axis against the averaged values of the quantifiable variable measured by the comparable methods (Bland and Altman 1999). However, when a reference standard method is used as a comparator to a new measurement method, the differences between the comparable methods can be plotted against the values of the examined variable measured by the reference standard method (Krouwer 2008). Based on the literature, the RIP was considered to be the reference standard monitoring method for breathing pattern measurements in this study (see section 4.2.4). Thus, the differences between the RIP and the SLP for each examined breathing component were allocated at y axis and plotted against values of breathing components as obtained by the RIP.

The 95% LOA of the Bland and Altman plots were calculated by using the mean difference between the paired measurements ± SD x 1.96 (Bland and Altman 1999). Measurement agreement between the comparable methods for each examined breathing component was determined when the majority of the differences between the paired measurements fell within 95%LOA, close to zero and along the middle reference line of the Bland and Altman plots, representing the mean difference between the RIP and the SLP.

5.2.11.2 Testing normality of the differences in the examined breathing components

The data were first examined to check for normal distribution of the differences for each examined breathing component between comparable methods at rest and after exercise. This was performed via histograms. A statistical test for checking normality was also used to confirm normality of the differences in breathing pattern data between the comparable methods. This statistical test was the Shapiro-Wilk test and it was used to examine whether the distribution of the differences in the examined breathing components between the comparable methods significantly deviated from a normal distribution either at rest or after exercise. Statistical significance level was 95% and if $p< 0.05$, the null hypothesis was rejected.

Differences in the examined breathing components between the RIP and the SLP including those after breath-by-breath analysis, were normally distributed apart from those for the RR, Ti, Te, Ttot at rest and those for the RR and RC_{amp} during both phases after exercise. This was determined by the presence of slightly skewed distributions of the above parameters as observed in histograms and confirmed by Shapiro Wilk T test. Because the slightly skewed distributions observed in some of the above parameters was found to be due to the presence of few outliers, normality of their

differences between the RIP and the SLP was assumed. This was based on a) the similarity of the shape of distributions of the parameterised values between the RIP and the SLP measurements, and b) the central limit theorem. This theorem states that a sampling distribution tends to be normal when a sample size is >30 although this assumption can be violated in heavily skewed and tailed distributions, which was not the case in this study (Wilcox 2005; Field 2009).

5.2.12 Pilot study

A pilot work was conducted to permit the researcher to familiarise himself with the equipment and to run through the protocol of the study. This gave the chance for identifying any potential problems during data collection. Successful data acquisition was performed during the pilot work. A member of the researcher's team acted as a participant for this pilot work. Breathing pattern data acquired during this pilot work enabled the researcher to further familiarise himself with the data extraction through the Matlab software prior to the actual data analysis and data extraction of this study.

5.2.13 Data protection and confidentiality among all studies undertaken in this research

The participants' anonymised demographic data, questionnaires and breathing pattern data were used by the researcher in each study of this research and shared only with his supervisors. Breathing pattern data were stored in a personal password protected computer accessible only by the researcher. An individual numerical code was allocated for each participant according to each study undertaken for the purposes of this research presented in this thesis. This was to ensure anonymity and for further data protection. Data files obtained in each study of this research were transferred into a PC computer within the School of Health Sciences, University of Southampton to be backed up. Personal data of participants (demographic and questionnaires) and signed consent forms of all studies conducted in this research were securely stored in a locked filing cabinet within the postgraduate research office of School of Health Sciences, University of Southampton.

5.3 The results of the validation study

5.3.1 Demographic data

Fifty adults (30 males) with mean age (sd) 29.26 years old (6.79 years) and mean BMI 23.44kg/m^2 (3.02kg/m^2) were enrolled in the study. The table below provides a summary of the individuals' demographic data and their averaged lung function measurements. According to the GINA

guidelines (2016), no airway obstruction was identified among the studied participants, all of whom were able to complete successfully the 10 minute submaximal exercise protocol on the cycle ergometer.

The same number of breath cycles was detected for each participant by both recording methods either at rest or after exercise. At rest, 3395 breath cycles pairs were detected in a sample of 50 adults. The mean number was 68 breath cycles with minimum and maximum being 35 and 110 respectively. As expected, more breath cycle pairs (n=4295) were detected after exercise. The mean number was 86 breath cycles with minimum and maximum being 46 and 135 respectively. For the breath-by-breath agreement between the RIP and the SLP, a total number of 7.690 breath cycle pairs were analysed as derived by summing up all the breath cycles detected at rest and after exercise within and between 50 individuals.

Table 5-1: The demographic data and the lung function measurements

Variable	μ	sd	Min	Max	95% CI Lower – upper	
Age (years)	29.26	6.79	21	48	27.33	31.19
Height (cm)	1.73	0.11	1.55	1.98	1.70	1.76
Weight (kg)	71.32	16.25	43.00	110.00	66.70	75.94
BMI (kg/m^2)	23.83	3.02	16.14	32.49	22.58	24.30
FEV_1 (L)	4.83	1.23	2.13	7.57	4.48	5.18
$FEV_{1predicted}$ (L)	3.78	0.81	2.34	5.18	3.55	4.01
FVC (L)	5.55	1.31	2.68	7.59	5.17	5.92
$FVC_{predicted}$ (L)	4.47	1.03	2.70	6.62	4.18	4.76
FEV_1/FVC (%)	85	6.00	78	96	83.70	87.11
$FEV_1/FVC_{predicted}$(%)	82	1.34	79	84	82.16	82.92

*__μ:__ mean value; **sd:** standard deviation; **Min:** minimum value; **Max:** maximum value; **95%CI:** 95% confidence intervals

5.3.2 The averaged agreement between the comparable methods for timing parameters at rest and after exercise

The Table 5-2 provides a summary of the mean differences (μ) and 95%LOA between the comparable methods for all timing parameters at rest and after exercise. Mean values of timing parameters as measured by each device at rest and after exercise are provided in Appendix C. The Bland and Altman plots for the RR, Ti, Te and Ttot are provided in the following sections. The Bland and Altman plots for the Ti/Te and Ti/Ttot are provided in Appendix C due to their similarity with the Bland and Altman plots of the other timing parameters and to avoid repetition.

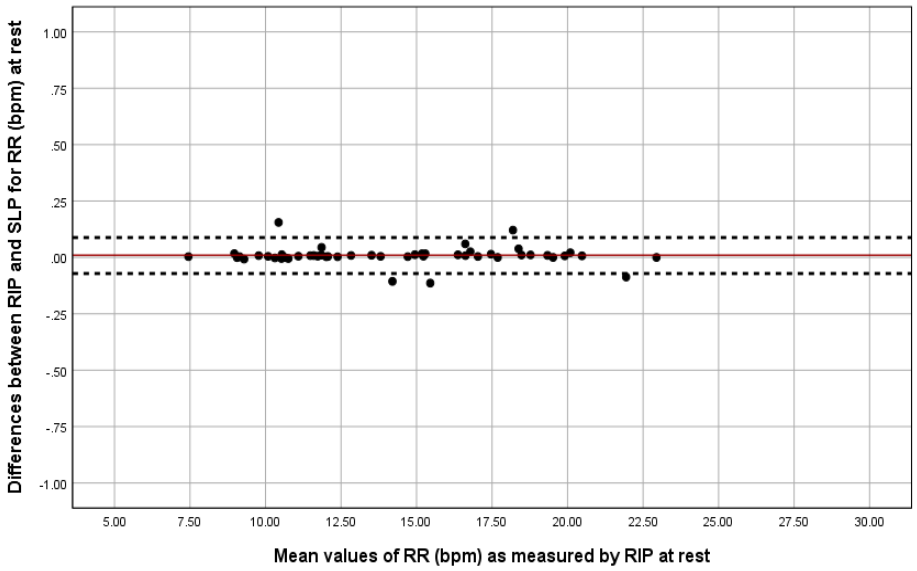
Good averaged agreement between the comparable methods for all timing parameters was found at rest (see plot a of Figure 5-6; Figure 5-7; Figure 5-8; Figure 5-9). Both monitoring methods measured nearly identical RR and Ttot and the largest mean difference between the RIP and the SLP was found for Te (μ: -0.03 sec, sd 0.09, 95%LOA [-0.21, -0.15]). The majority of the differences (≥ 92%) for all the examined timing parameters fell within narrow 95% LOA and close to zero suggesting good agreement between the comparable methods. The differences in all timing parameters fell also along the middle reference line of the Bland and Altman plots. There was not a systematic tendency of them towards becoming either larger or smaller over the several ranges of magnitudes of the examined timing components obtained by the RIP.

The results obtained after exercise were consistent with those found at rest. The RR was significantly increased after exercise and this was found for both devices (RIP: μ -3.57 bpm, 95%CI [-4.41, -2.73], p 0.000; SLP:μ -3.57, 95%CI [-4.41, -2.73], p 0.000). A summary of the mean differences in each timing component between resting breathing and after exercise as measured separately by each device is provided in Appendix C. Good averaged agreement between the RIP and the SLP was maintained for the examined timing components after exercise (see plot b of Figure 5-6, Figure 5-7, Figure 5-8, Figure 5-9). Closer agreement between the comparable methods was found for all timing components with mean differences between the RIP and the SLP being smaller compared to those found at rest. The majority of the differences (≥ 96%) between the RIP and the SLP still fell close to zero and along the middle reference line of the Bland and Altman plots within narrower 95% LOA compared to those found at rest.

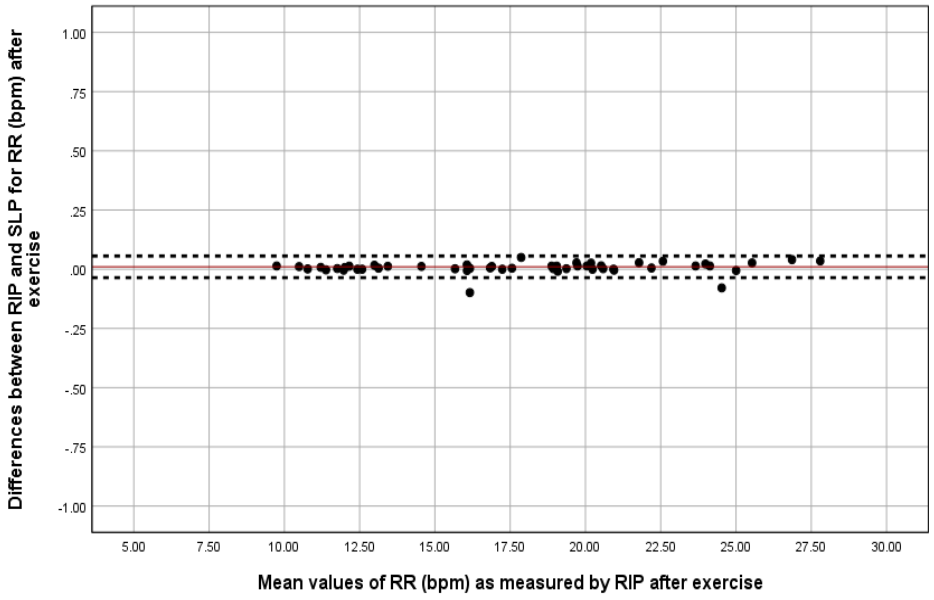
Table 5-2: Mean differences and 95% limits of agreement between Respiratory Inductive Plethysmography and Structured Light Plethysmography for timing parameters at rest and after exercise

	Mean differences between RIP and SLP at rest			**Mean differences between RIP and SLP after exercise**		
Breathing component	***μ (sd)**	***95%CI Lower-Upper**	***95%LOA Lower-upper**	**μ (sd)**	**95%CI Lower-upper**	**95%LOA Lower-upper**
RR (bpm)	0.01 (0.04)	-0.01 0.02	-0.07 – 0.09	0.01 (0.02)	0.00 0.01	-0.03 – 0.05
Ti (sec)	0.02 (0.09)	0.00 0.05	-0.15 – 0.19	-0.01 (0.04)	-0.02 0.00	-0.09 – 0.07
Te (sec)	-0.03 (0.09)	-0.05 0.00	-0.21 – 0.15	0.01 (0.04)	0.00 0.02	-0.07 – 0.09
Ttot (sec)	-0.01 (0.02)	-0.01 0.00	-0.04 – 0.02	0.00 (0.01)	-0.01 0.02	-0.01 – 0.01
Ti/Te	0.01 (0.06)	0.00 0.03	-0.11 – 0.13	-0.01 (0.04)	-0.02 0.00	-0.08 – 0.06
Ti/Ttot	0.00 (0.02)	0.00 0.01	-0.37 – 0.37	0.00 (0.01)	-0.01 0.00	-0.02 – 0.02

***μ**: mean difference, **sd:** standard deviation; **95%CI**: 95% confidence intervals; **95%LOA**: 95% limits of agreement

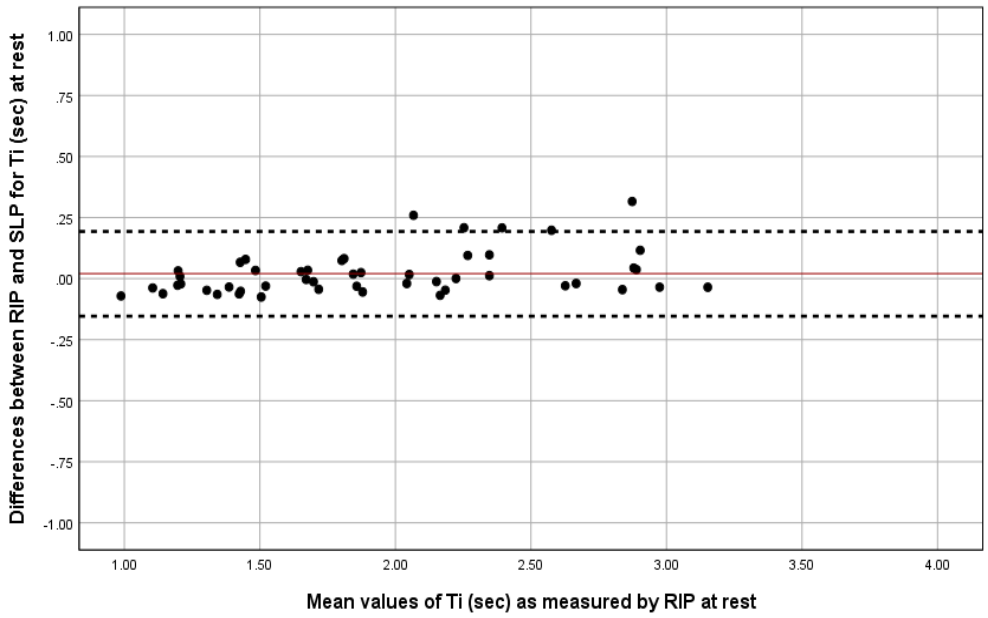


(a)

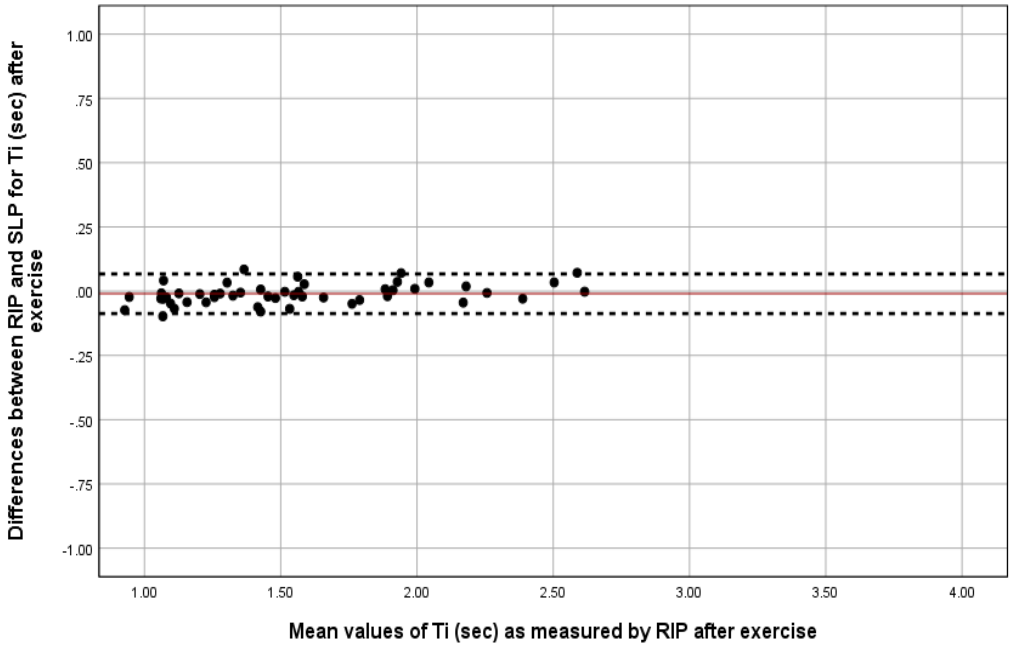


(b)

Figure 5-6: The Bland and Altman plots for the RR at rest (plot a) and after exercise (plot b). The mean difference between the RIP and the SLP (red line) was found to be 0.01bpm either at rest or after exercise. The black dashed lines above and below the red line represent the upper and lower limits of agreement.

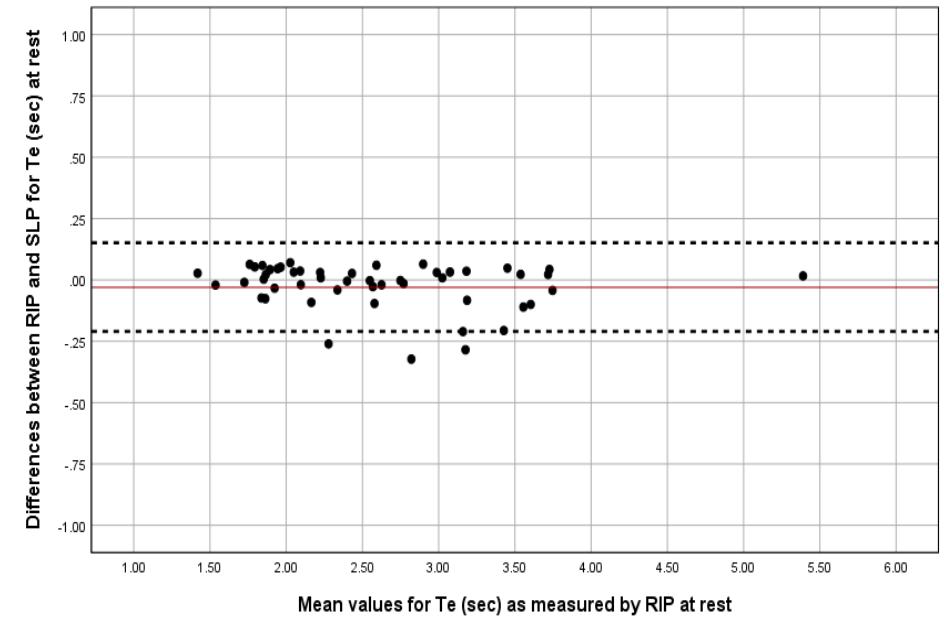


(a)

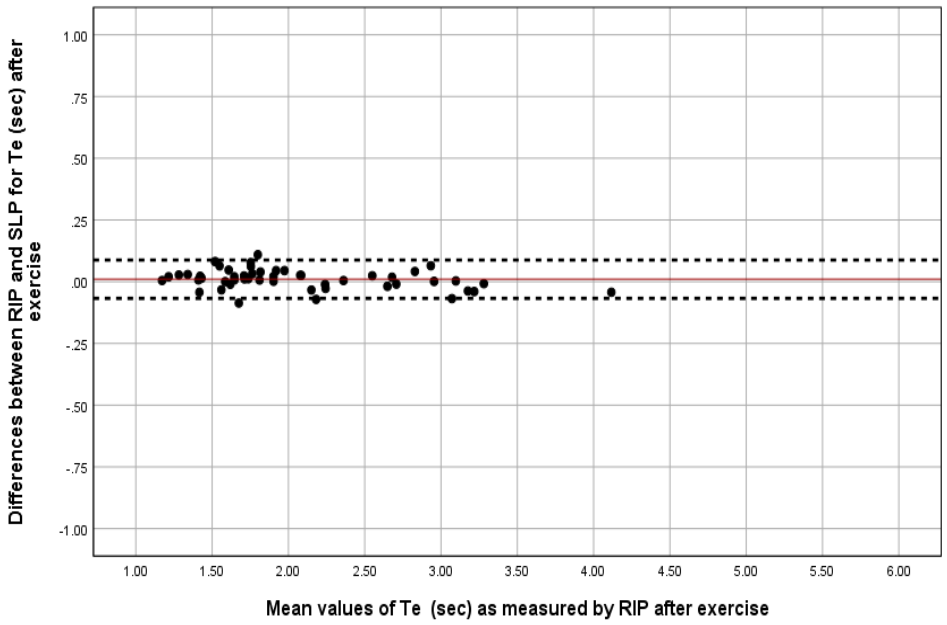


(b)

Figure 5-7: The Bland and Altman plots for the Ti at rest (plot a) and after exercise (plot b). The mean difference between the RIP and the SLP (red line) was found to be 0.02 seconds at rest and -0.01 seconds after exercise. The black dashed lines above and below the red line represent the upper and lower limits of agreement.

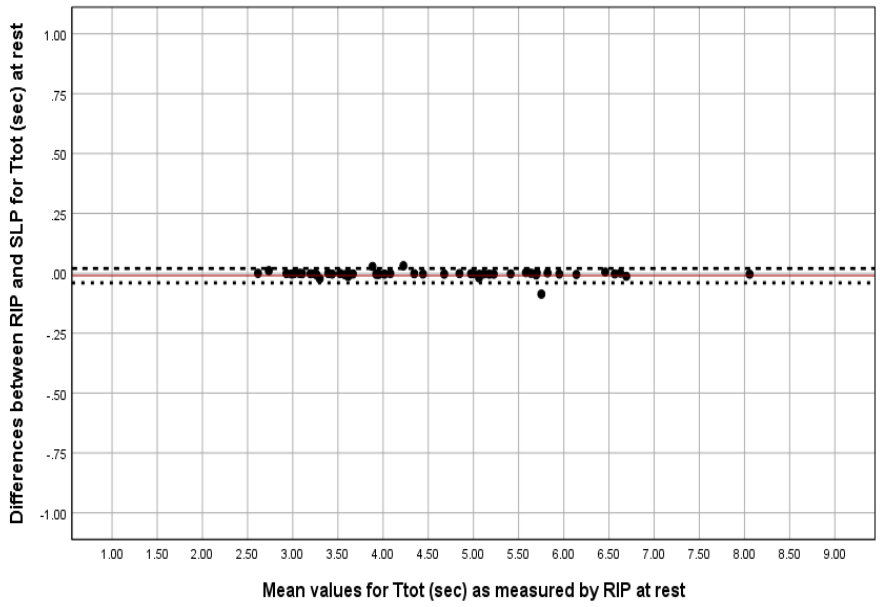


(a)

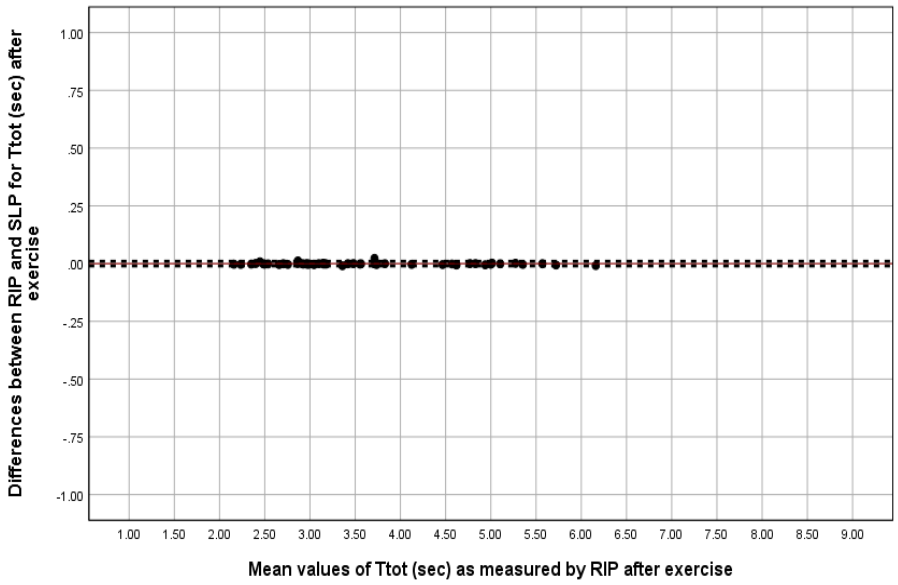


(b)

Figure 5-8: The Bland and Altman plots for the Te at rest (plot a) and after exercise (plot b). The mean difference between the RIP and the SLP (red line) was found to be -0.03 seconds at rest and 0.01 seconds after exercise. The black dashed lines above and below the red line represent the upper and lower limits of agreement.



(a)



(b)

Figure 5-9: The Bland and Altman plots for the Ttot at rest (plot a) and after exercise (plot b). The mean difference between the RIP and the SLP (red line) was found to be -0.01 seconds at rest and 0.00 seconds after exercise. The black dashed lines above and below the red line represent the upper and lower limits of agreement.

5.3.3 The breath-by-breath agreement between the comparable methods for the timing parameters

The Table 5-3 summarises the mean differences and 95%LOA between the RIP and the SLP for timing parameters as found after a breath-by-breath analysis from before to after exercise within

and between 50 individuals. Breath-by-breath analysis allowed the examination of the measurement agreement between the devices over a greater range of magnitudes of examined breathing components as obtained by the RIP than these found at rest and after exercise (see Table 5-4).

Good breath-by-breath agreement was found for all timing parameters over a greater range of magnitudes of those parameters. The mean difference in the Ti, Te and Ttot between the comparable methods was 0.00 seconds. According to the Bland and Altman plots, the majority of the differences fell within or close to the 95%LOA. Only in the Bland and Altman plot for the Ti, it can be noticed that the differences between the RIP and the SLP could become bigger when the Ti was >4 seconds as measured by the RIP. However, when the Ti was >4 seconds the majority of the differences between the devices (23 out of 36) fell within 95%LOA (see Figure 5-10).

Table 5-3: Mean differences and 95% limits of agreement between the comparable methods for timing parameters after a breath-by-breath analysis (no of breath cycles= 7690)

Breathing component	***μ (sd)**	***95% CI Lower-upper bound**	***95%LOA Lower- upper limit**
Ti (sec)	0.00 (0.24)	-0.01 – 0.00	-0.47 – 0.47
Te (sec)	0.00 (0.30)	-0.01 – 0.00	-0.58 – 0.58
Ttot (sec)	0.00 (0.36)	-0.01 – 0.00	-0.70 – 0.70
Ti/Te	-0.01 (0.17)	-0.01 – 0.00	-0.34 – 0.32
Ti/Ttot	0.00 (0.04)	0.00 – 0.00	-0.08 – 0.08

***μ:** mean difference: **sd:** standard deviation; **95%CI:** 95% confidence intervals; **95%LOA:** 95% limits of agreement

Table 5-4: Minimum and maximum values of timing parameters obtained by the Respiratory Inductive Plethysmography at rest, after exercise and after a breath-by-breath analysis.

	At rest		After exercise		Breath-by-breath analysis	
Variable	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Ti (sec)	0.99	3.15	0.93	2.62	0.30	6.37
Te (sec)	1.42	5.39	1.17	4.12	0.30	13.33
Ttot (sec)	2.62	8.06	2.16	6.16	0.63	14.36
Ti/Te	0.49	1.24	0.50	1.19	0.08	3.71
Ti/Ttot	0.33	0.55	0.33	0.54	0.07	0.79

Min: minimum; **Max:** maximum

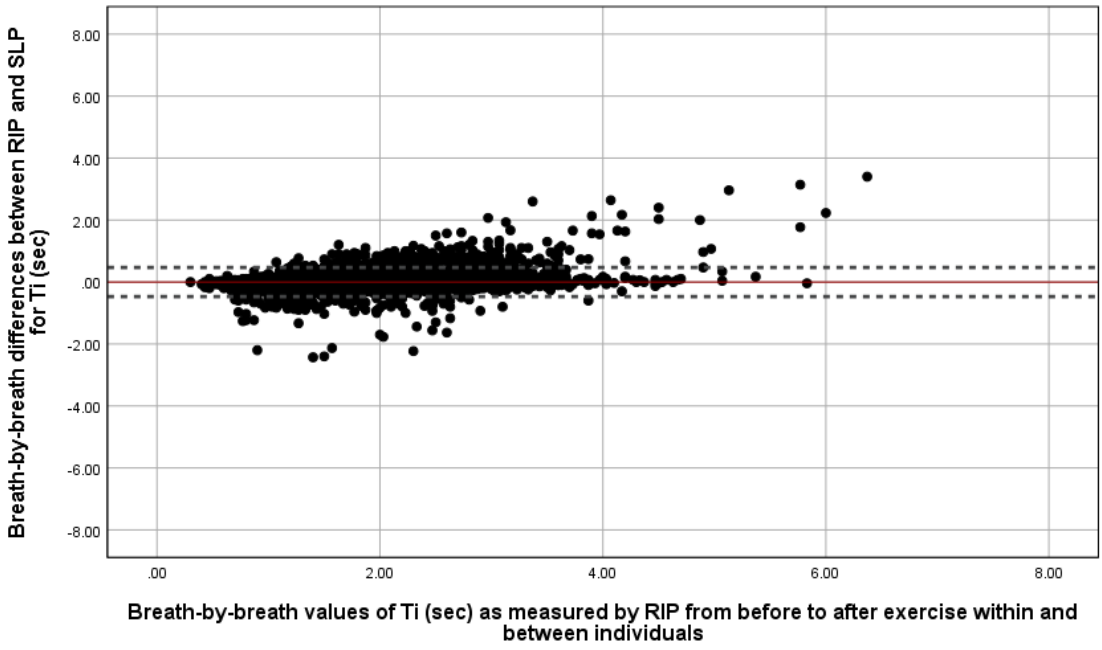


Figure 5-10: The Bland and Altman plot for the Ti showing the breath-by-breath agreement between the comparable methods. The mean difference between the RIP and the SLP (red line) was found to be 0.00 seconds. The grey dashed lines represent the upper and lower 95%LOA respectively.

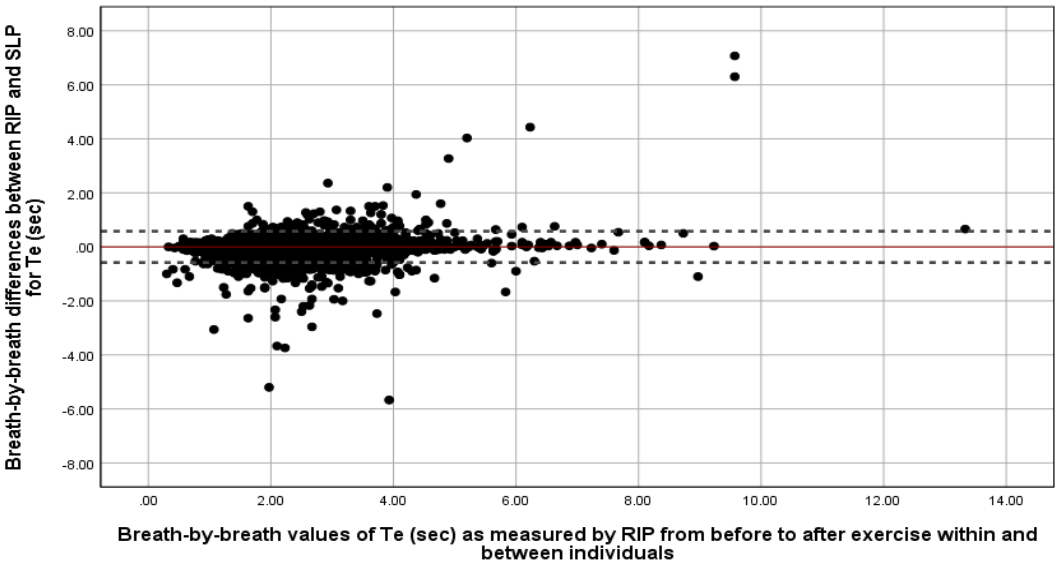


Figure 5-11: The Bland and Altman plot for the Te showing the breath-by-breath agreement between the comparable methods.The mean difference between the RIP and the SLP (red line) was found to be 0.00 seconds. The grey dashed lines represent the upper and lower 95%LOA respectively.

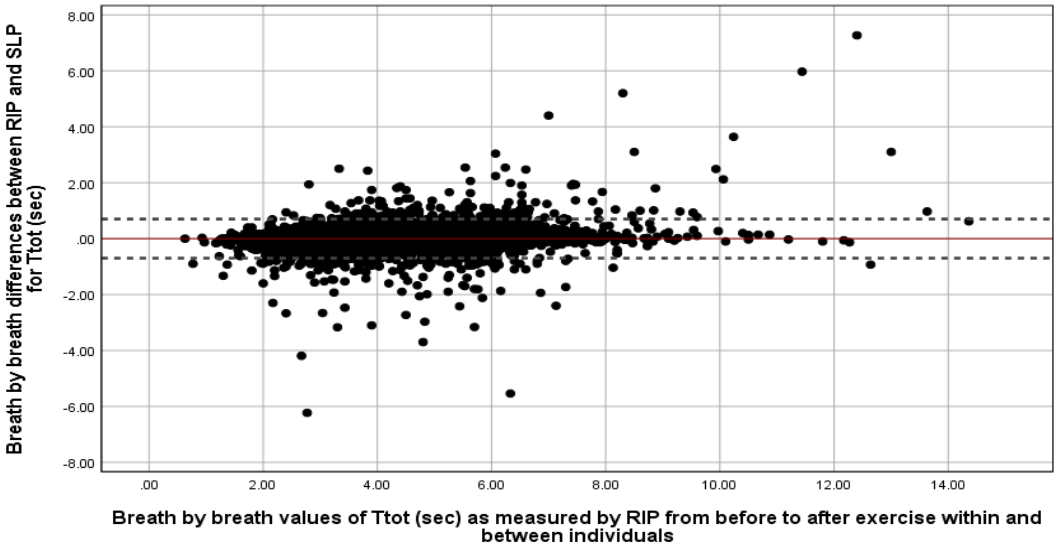


Figure 5-12: The Bland and Altman plot for the Ttot showing the breath-by-breath agreement between the comparable methods. The mean difference between the RIP and the SLP (red line) was found to be 0.00 seconds. The grey dashed lines represent the upper and lower limits of agreement.

5.3.4 The averaged agreement between the comparable methods for the changes in timing parameters after exercise

The Table 5-5 provides a summary of the mean differences (plus 95% LOA) between the RIP and the SLP for the changes in timing parameters after exercise. The SLP recorded an increase of the RR and decrease of the Ti, Te and Ttot after exercise and these changes were in accordance with those recorded by the RIP after exercise (see Appendix C). The larger mean difference between the RIP and the SLP for the changes in timing parameters after exercise was found for Ti and Te (see Table 5-5). Good averaged agreement between the devices was found for the changes in all timing components after exercise (see Figure 5-13, Figure 5-14, Figure 5-15, Figure 5-16). The majority of the differences (> 88%) fell within narrow 95%LOA and along the middle reference line of the Bland and Altman plots indicating no systematic bias between the comparable methods.

Table 5-5: Mean differences and limits of agreement between the comparable methods for the changes in timing parameters after the exercise

Breathing parameter	***μ (sd)**	***95%CI Lower-Upper bound**	***95%LOA Lower-upper limit**
RR (bpm)	0.00 (0.05)	-0.01 – 0.01	-0.09 – 0.09
Ti (sec)	0.03 (0.07)	0.01 – 0.05	-0.12 – 0.18
Te (sec)	-0.03 (0.07)	-0.05 - -0.01	-0.18 – 0.12
Ttot (sec)	0.00 (0.01)	-0.01 – 0.00	-0.03 – 0.03
Ti/Te	0.02 (0.05)	0.01 – 0.04	-0.08 – 0.12
Ti/Ttot	0.01 (0.02)	0.00 – 0.01	-0.02 – 0.04

***μ:** mean difference; **95%CI:** 95% confidence intervals, **95%LOA:** 95% limits of agreement

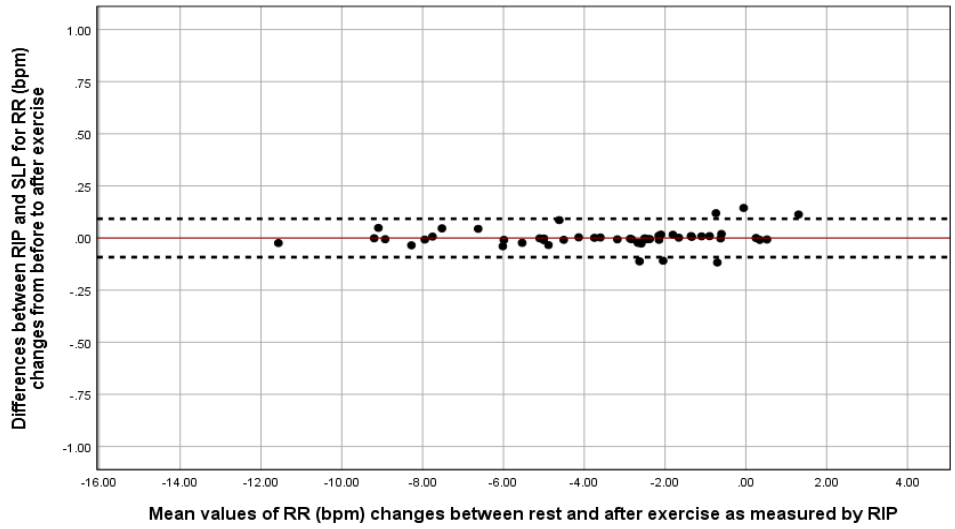


Figure 5-13: The Bland and Altman plot for the changes in RR showing the agreement between the comparable methods after the exercise. Negative values in the x axis show increase of the RR as recorded by the RIP after the exercise. The red line represents the mean difference between the methods (μ 0.00 bpm). The black dashed lines above and below the red line represent the upper and lower limit of agreement.

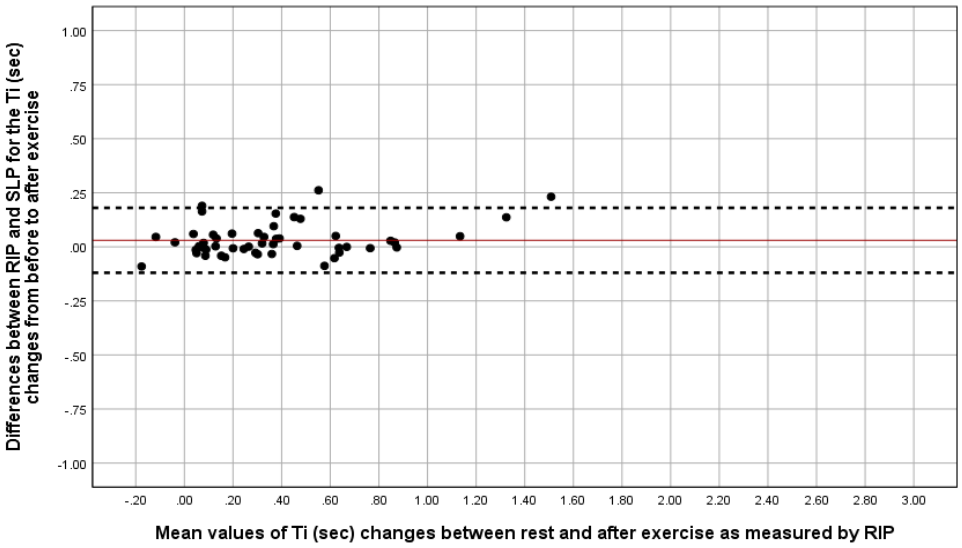


Figure 5-14: The Bland and Altman plot for the changes in Ti showing the agreement between the comparable methods after the exercise. Negative values in the x axis show increase in Ti as recorded by the RIP after the exercise. The red line represents the mean difference between methods (μ 0.03 seconds). The black dashed lines above and below the red line represent the upper and lower limit of agreement.

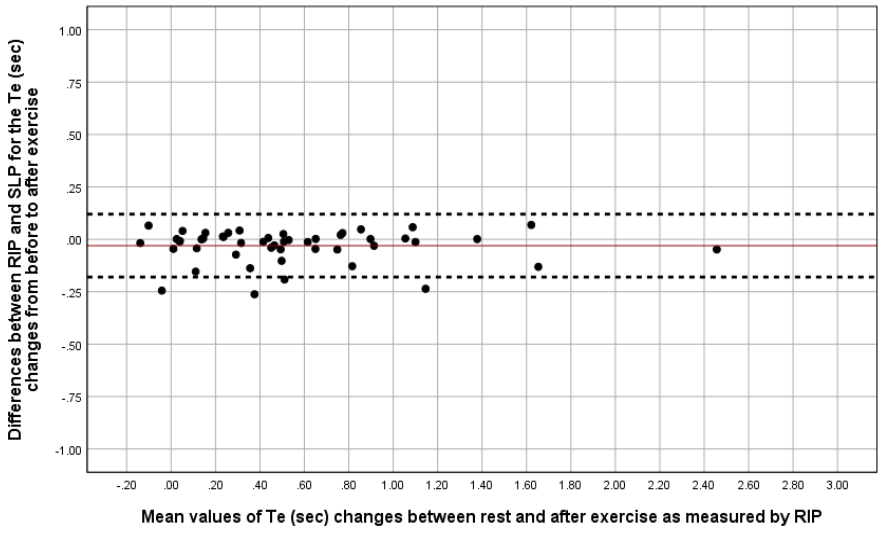


Figure 5-15: The Bland and Altman plot for the changes in Te showing the agreement between the comparable methods after exercise. Negative values on the x axis show increase in the Te as measured by the RIP after exercise. The red line represents the mean difference between methods (μ -0.03 seconds). The black dashed lines above and below the red line represent the upper and lower limit of agreement.

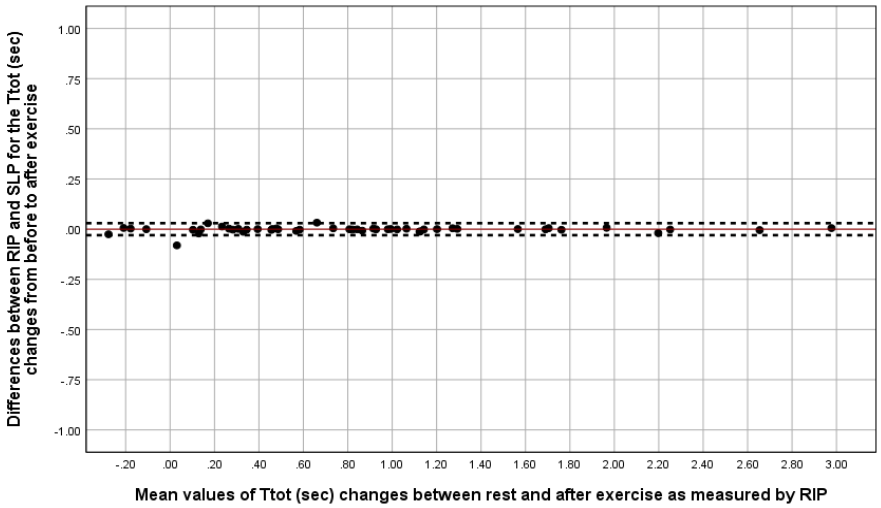


Figure 5-16: The Bland and Altman plot for the changes in Ttot showing the agreement between the comparable methods after the exercise. Negative values on the x axis show increase in the Ttot as measured by the RIP after exercise. The red line represents the mean difference between methods (μ 0.00 sec). The black dashed lines above and below the red line represent the upper and lower limits of agreement.

5.3.5 The averaged agreement between the comparable methods for the thoracoabdominal movements at rest and after exercise

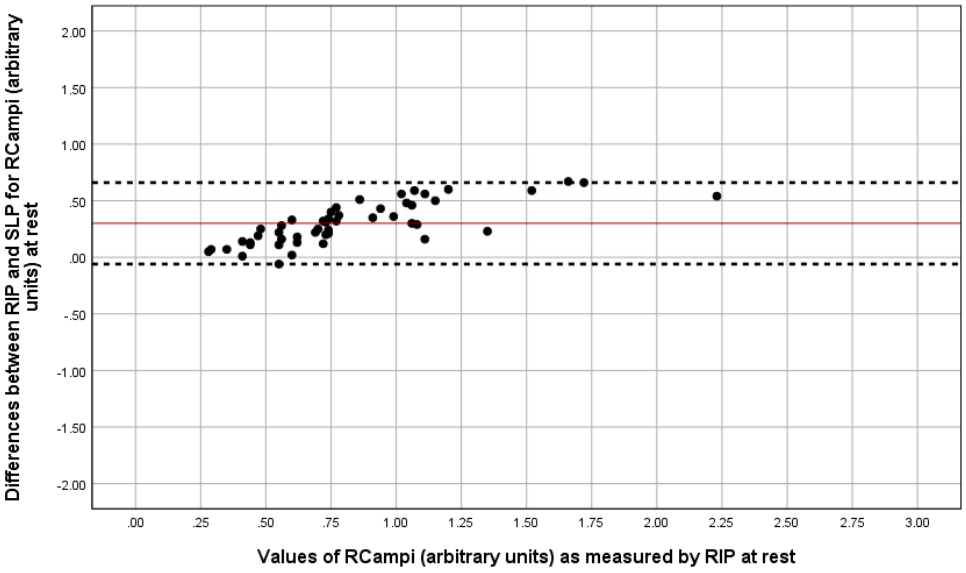
In the following sections, only the results of the RC_{amp}, the AB_{amp} and the RC_{amp}/AB_{amp} during the inspiration phase are provided. This is due to their similarity with those found during the expiration phase. The results of the expiration phase are provided in the Appendix C to avoid repetition. The Table 5-6 provides a summary of the mean differences in the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins} between the RIP and the SLP both at rest and after exercise. Their mean values as recorded by each device at rest and after exercise are provided in the Appendix C.

Larger mean differences between the comparable methods were found for the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins} after exercise compared to those found at rest. Although the differences in the RC_{ampins} and the AB_{ampins} fell within 95%LOA, a tendency of greater discrepancy between devices could be observed over greater magnitudes of these parameters (see Figure 5-17, Figure 5-18, plots a). This was consistent after exercise, as the observed differences between the methods fell out of larger 95%LOA over greater magnitudes of the RC_{ampins} (>1.75 arbitrary units) and the AB_{ampins} than those found at rest(>1.50 arbitrary units) (see Figure 5-17, Figure 5-18, plots b). In contrast, good agreement between the RIP and the SLP was found for the RC_{ampins}/AB_{ampins} both at rest and after the exercise. The majority of the differences (96%) fell close to zero, along the middle reference line of the Bland and Altman plot and within 95%LOA (see Figure 5-19, plot a). This was consistent to what was found after exercise (see Figure 5-19, plot b) despite slightly larger 95%LOA.

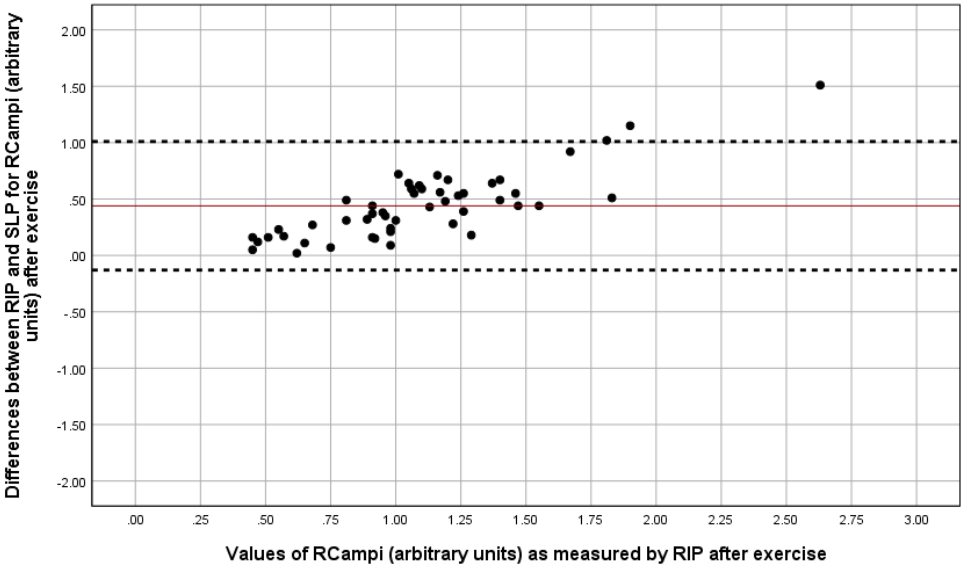
Table 5-6: Mean differences and 95% limits of agreement between the comparable methods for the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins} both at rest and after exercise

	Mean differences between RIP and SLP at rest			**Mean differences between RIP and SLP after exercise**		
Breathing component	***μ (sd)**	***95%CI Lower-Upper**	***95%LOA Lower-upper**	**μ (sd)**	**95%CI Lower-upper**	**95%LOA Lower-upper**
RC_{ampins} (arbitrary units)	0.31 (0.18)	0.25-0.35	-0.06-0.66	0.44 (0.29)	0.36-0.52	-0.13-1.01
AB_{ampins} (arbitrary units)	0.23 (0.15)	0.19-0.27	-0.06-0.52	0.29 (0.20)	0.23-0.34	-0.10-0.68
RC_{ampins}/AB_{ampins}	0.03 (0.21)	-0.03-0.09	-0.33-0.44	0.10 (0.24)	0.03-0.17	-0.38-0.58

***μ:** mean difference, **sd:** standard deviation; **95%CI**: 95% confidence intervals; **95%LOA**: 95% limits of agreement

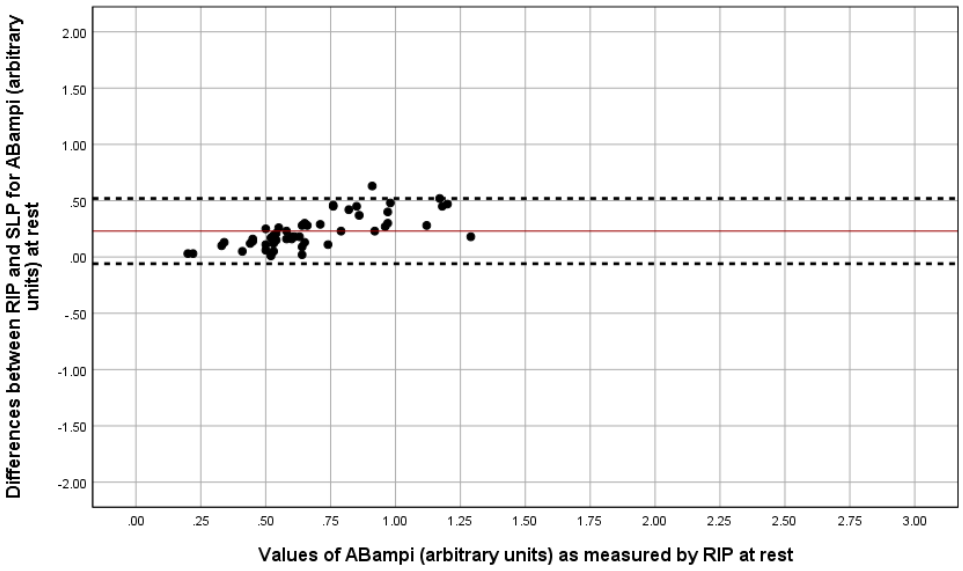


(a)

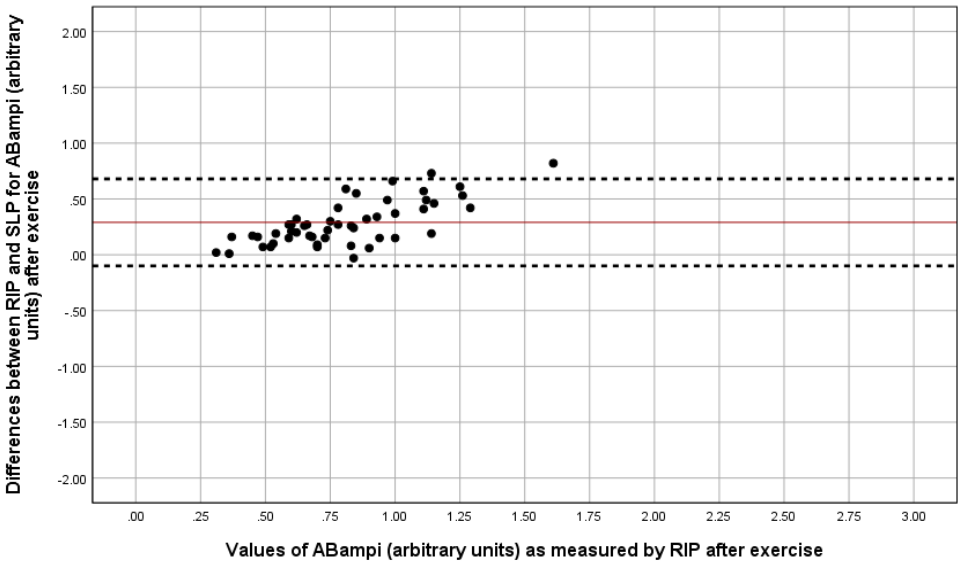


(b)

Figure 5-17: The Bland and Altman plot for the RC_{ampins} at rest (plot a) and after the exercise (plot b). The mean difference between the methods (red line) was found to be 0.31 arbitrary units at rest and 0.44 arbitrary units after the exercise. The black dashed lines show the upper and lower limit of agreement respectively.

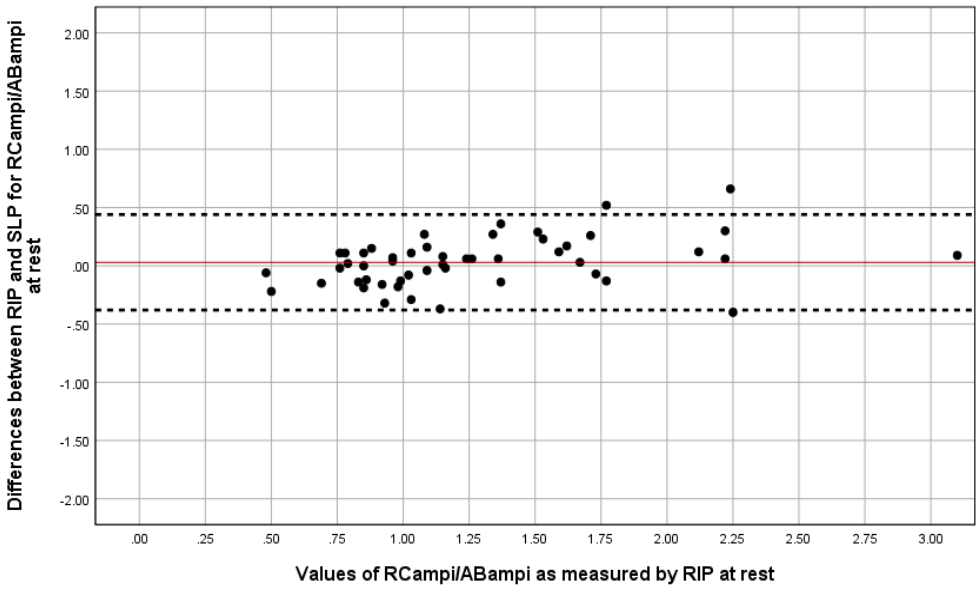


(a)

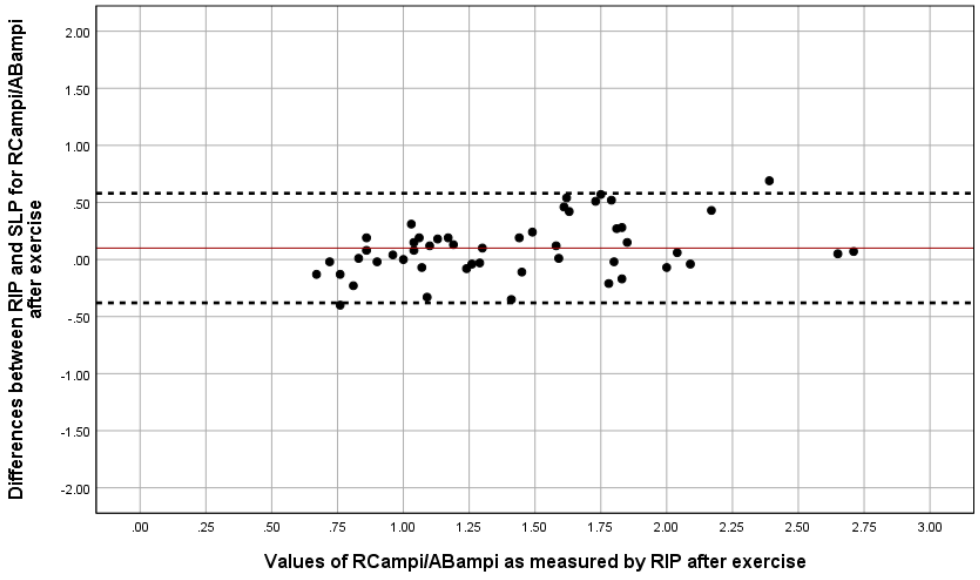


(b)

Figure 5-18: The Bland and Altman plot for the AB_{ampins} at rest (plot a) and after exercise (plot b). The mean difference between the methods (red line) was found to be 0.23 arbitrary units at rest and 0.29 arbitrary units after the exercise. The black dashed lines show the upper and lower limit of agreement respectively.



(a)



(b)

Figure 5-19: The Bland and Altman plot for the RC_{ampins}/AB_{ampins} at rest (plot a) and after exercise (plot b). The mean difference between the methods (red line) was found to be 0.03 at rest and 0.10 after exercise. The black dashed lines show the upper and lower limit of agreement respectively

5.3.6 The breath-by-breath agreement between the comparable methods for the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins}

The Table 5-7 summarises the mean differences between the RIP and the SLP for the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins} after the breath-by-breath analysis including all breath cycles detected from before to after exercise within and between 50 individuals. A discrepancy between the comparable methods was found to measure the RC_{ampins} and the AB_{ampins} over greater magnitudes of these parameters as measured by the RIP (see Figure 5-20 and Figure 5-21). The differences between the methods systematically tended to become larger and fell out of the 95%LOA over greater RC_{ampins} and AB_{ampins}. In contrast, there was a good breath-by-breath agreement for the RC_{ampins}/AB_{ampins} (see Figure 5-22) as similarly found when averaged agreement between the RIP and the SLP was checked either at rest or after exercise.

Table 5-7: Mean differences and 95% limits of agreement between the comparable methods for the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins} after a breath-by-breath analysis (n=7690 breath cycles)

Breathing component	***μ (sd)**	**˜95% CI Lower-upper bound**	**&95%LOA Lower- upper limit**
RC_{ampins} (arbitrary units)	0.43 (0.31)	0.43-0.44	-0.19-1.05
AB_{ampins} (arbitrary units)	0.28 (0.21)	0.27-0.28	-0.13-0.69
RC_{ampins}/AB_{ampins}	0.12 (0.69)	0.11-0.14	-1.23-1.47

***μ:** mean difference; **sd:** standard deviation; **95%CI:** 95% confidence intervals; **95%LOA**: 95% limits of agreement

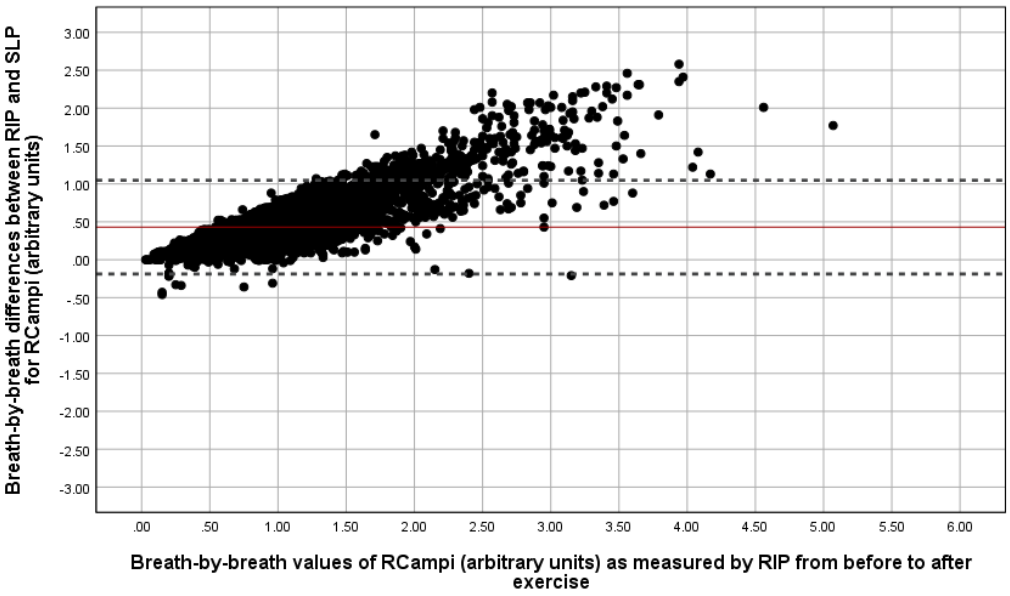


Figure 5-20: The Bland and Altman plot for the RC_{ampins} showing the breath-by-breath agreement between the comparable methods.

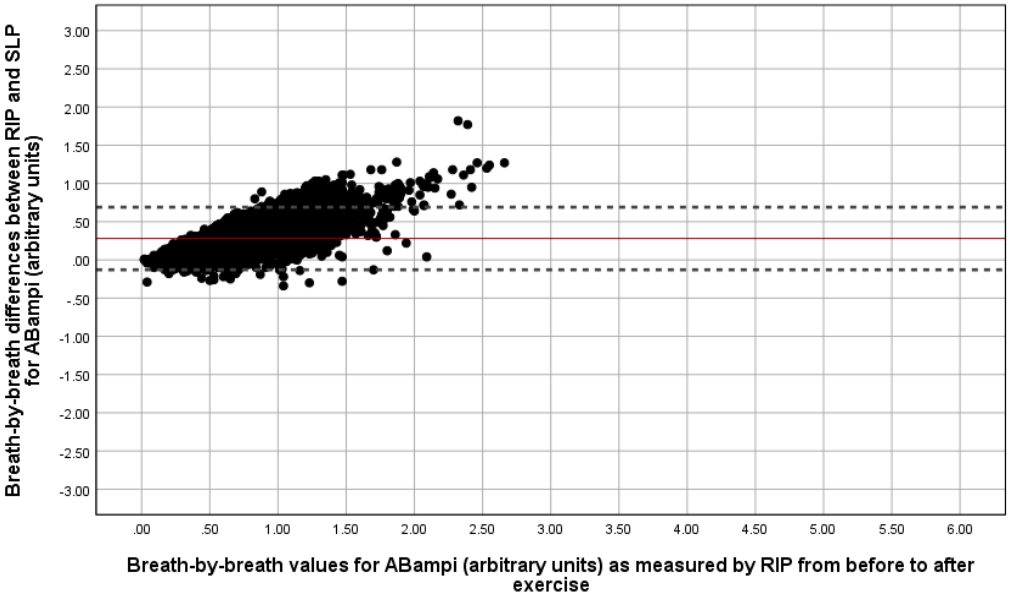


Figure 5-21: The Bland and Altman plot for the AB_{ampins} showing the breath-by-breath agreement between the comparable methods.

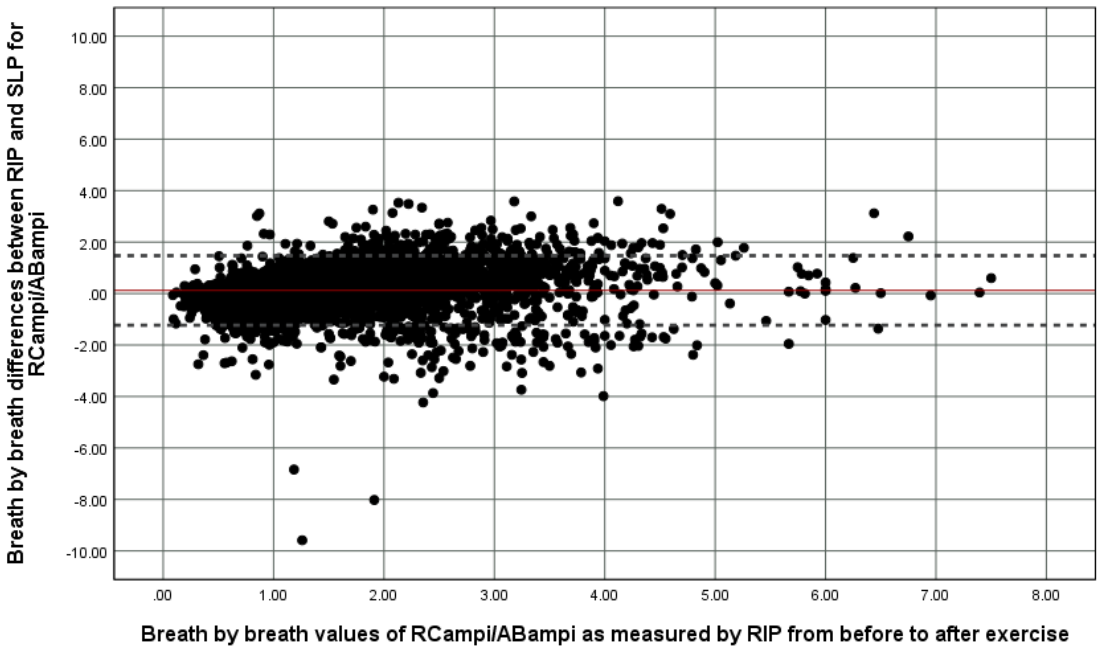


Figure 5-22: The Bland and Altman plot for the RC_{ampins}/AB_{ampins} showing the breath-by-breath agreement between the comparable methods

5.3.7 The averaged agreement between the comparable methods for the changes in the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins}

The Table 5-8 provides a summary of the mean differences between the RIP and the SLP for the changes in the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins} after exercise. The mean values of the changes in these parameters as measured by each device are provided in the Appendix C. In overall, the RC_{ampins} was increased (μ -0.26 sd 0.28 95%CI [-0.18, -0.05]) after exercise as measured by the RIP and this was in accordance with the SLP measurements (μ-0.13 sd 0.19 95%CI [-0.18, -0.07]). Both comparable methods showed a relative averaged increase in the AB_{ampins} and both of them showed averaged greater RC_{ampins}/AB_{ampins} after the exercise.

The differences of the changes in the RC_{ampins} and the AB_{ampins} between the comparable methods were tended to increase over greater magnitudes of changes in these parameters, but this was not found for the RC_{ampins}/AB_{ampins} (see Figure 5-23, Figure 5-24, Figure 5-25). However, the majority of the differences (94%) of the changes in all the above parameters between the methods fell within 95%LOA.

Table 5-8: Mean differences and 95% limits of agreement between the comparable methods for the changes in the RC_{ampins}, the AB_{ampins} and the RC_{ampins}/AB_{ampins} after exercise

Breathing component	***μ (sd)**	***95%CI Lower-Upper bound**	***95%LOA Lower-upper limit**
RC_{ampins} (arbitrary units)	-0.14 (0.24)	-0.21- -0.07	-0.60-0.32
AB_{ampins} (arbitrary units)	-0.05 (0.16)	-0.10- -0.01	-0.37-0.27
RC_{ampins}/AB_{ampins}	-0.06 (0.21)	-0.13- 0.00	-0.50-0.38

* **μ:** mean difference; **sd:** standard deviation; **95%CI:** 95% confidence intervals**; 95%LOA:** 95% limits of agreement

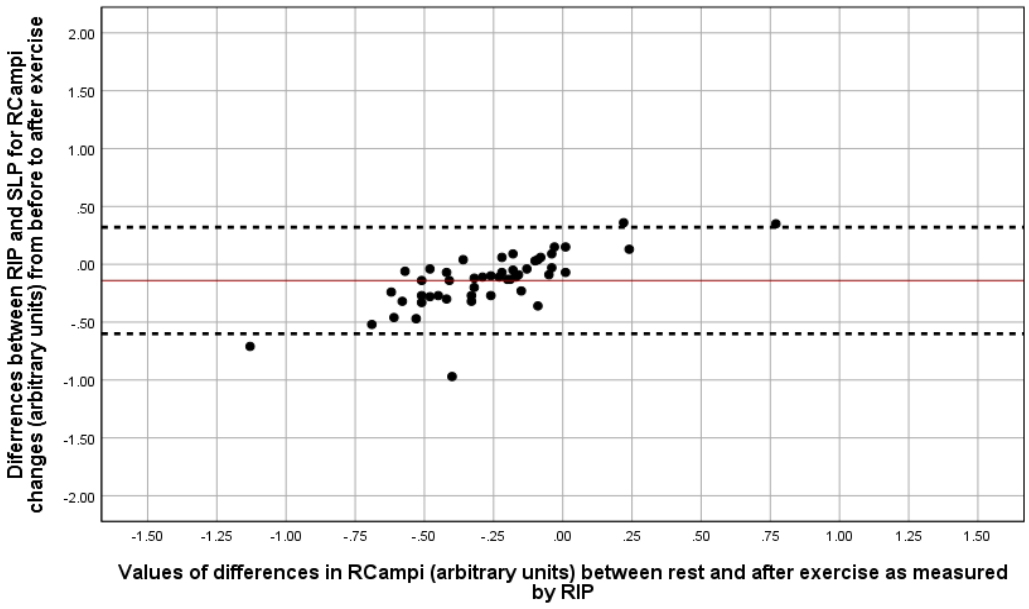


Figure 5-23: The Bland and Altman plot for the changes in the RC_{ampins} showing the agreement between the comparable methods after exercise. Negative values in the x axis show an increase in the RC_{ampins} after exercise.

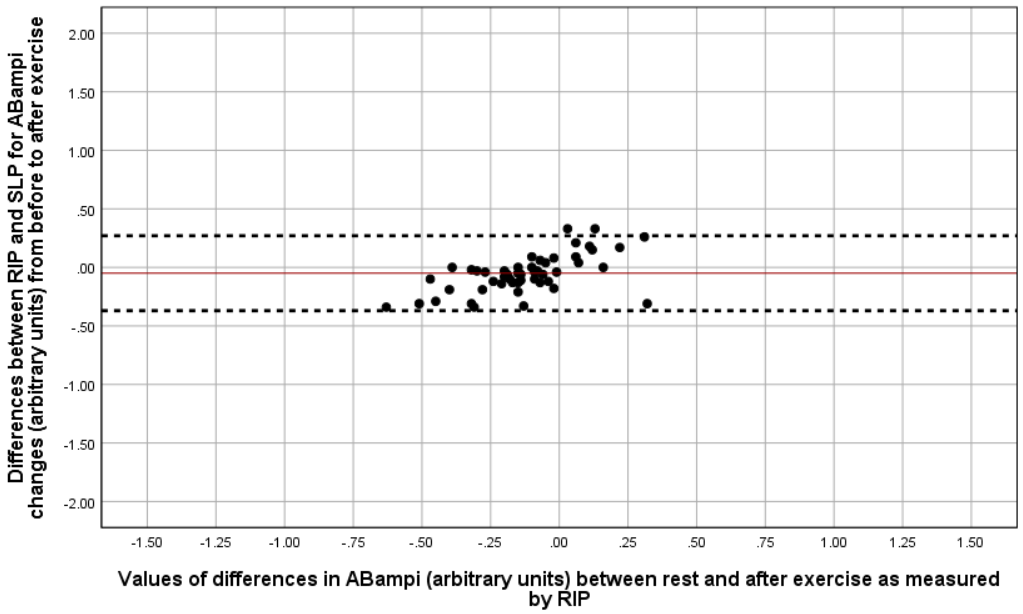


Figure 5-24: The Bland and Altman plot for the changes in the AB_{ampins} showing the agreement between the comparable methods after exercise. Negative values in the x axis show an increase in the AB_{ampins} after exercise.

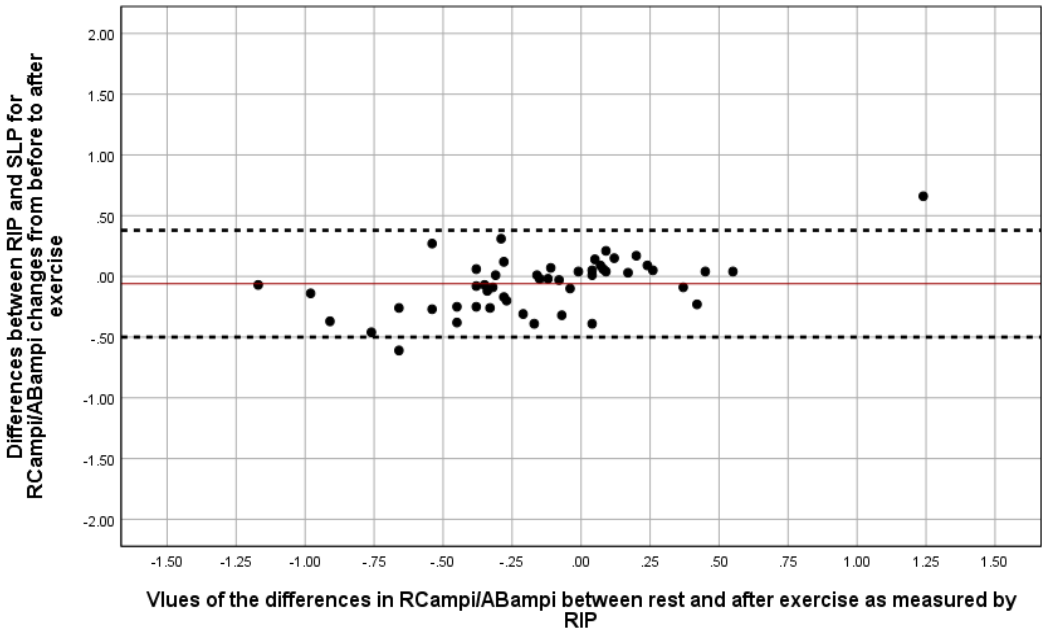


Figure 5-25: The Bland and Altman plot for the changes in the RC_{ampins}/AB_{ampins} showing the agreement between the comparable methods after exercise. Negative values in the x axis show an increase in the RC_{ampins}/AB_{ampins}

5.4 Discussion of the findings

5.4.1 The accuracy of the Structured Light Plethysmography under different breathing conditions

This validation study aimed to determine the SLP's accuracy for breathing pattern components during different breathing conditions compared to the RIP. The study's results suggest that the SLP can be considered as an accurate and responsive monitoring method for estimating timing parameters of breathing patterns during not only resting breathing but also during rapid breathing. Motamedi-Fakhr et al (2017b) have previously reported that the SLP accurately records timing parameters during resting breathing. This is in agreement with the results found in the validation study presented here. Motamedi-Fakhr et al (2017b) stated that there was an agreement between the SLP and the PNT for timing parameters, such as the RR, the Ti, the Te, the Ti/Te and the Ti/Ttot, in a sample involving healthy adults and patients with COPD or asthma. However, in their study, the accuracy of the SLP was assessed only during resting breathing within a relatively short-time period (45 seconds). The study presented here further supports the SLP's accuracy at recording timing parameters over longer periods of time. The mean differences (plus 95%LOA) between the RIP and the SLP for all timing parameters were similar to those found between the PNT and the SLP as reported by Motamedi-Fakhr et al (2017b). The authors proposed that a mean difference <0.5 seconds for non-ratio timing parameters was not likely to be considered clinically significant. In the study presented here, all the mean differences between the RIP and the SLP for these timing components were found to be less 0.5 seconds.

The validation study has added to our current knowledge regarding the SLP's performance, because agreement between the RIP and the SLP for timing parameters was additionally found during faster breathing rather than resting breathing. The SLP was found to be able to measure timing parameters after submaximal exercise when compared to the RIP. The exercise was used as a means to increase the RR within individuals as it can be present in respiratory diseases, such as asthma (Barker and Everard 2015). The mean difference between the RIP and the SLP for the RR during both resting breathing and after exercise was found to be smaller than the reported clinically important difference of 2 bpm (Smith et al. 2011; Motamedi-Fakhr et al. 2017b). Furthermore, breath-by-breath agreement was found between the comparable methods for all timing parameters, further supporting the ability of the SLP to record timing parameters in a wider variety of breath volumes. Also the within-individual variability of breathing patterns did not change the results of the measurement agreement between the RIP and the SLP.

Motamedi-Fkhr et al. (2017a) had previously supported that SLP can detect differences in timing parameters between healthy adults and patients with COPD. Although the SLP was reported to show some responsiveness to change in response to this pathology, these changes were not validated against other monitoring technologies. The validation study presented here can further expand our knowledge regarding the SLP's responsiveness. The SLP could record changes in timing parameters after exercise and these changes were almost identical to those recorded by the RIP irrespective of the different recording approaches used by the two methods. However, contradictory results were observed in terms of the SLP's accuracy to measure individual RC_{amp} and AB_{amp} during both respiratory phases compared to the RIP.

The ability of SLP to measure contributions of the RC and the AB to THA motion has been previously examined only by Elshafie et al. (2016) in a small (n=15) feasibility study. This study involved the recording of THA movements before and after lung resection surgery. The authors reported that there were statistically significant post-operative reductions in the RC contributions to THA motion compared to pre-operative measurements, supporting the SLP to be a responsive instrument. In the study presented here, where direct comparisons of the SLP's RC_{amp} and AB_{amp} were sought compared to those obtained by the RIP, the SLP tended to give smaller measurements of these parameters than the RIP. This was especially observed in faster breathing rates at the analysis of the breath-by-breath agreement between the comparable methods. A tendency towards bigger discrepancies between the comparable methods were identified over greater magnitudes of the RC_{amp} and the AB_{amp} as measured by the RIP.

These findings depend on accepting the RIP as a reference standard monitoring method for quantifying compartmental displacements of THA movements. To date, none of the available non-invasive recording methods have been compared in terms of the regional quantification of the RC and the AB displacements. As seen in chapter 4, current non-invasive recording methods, such as the RIP and the OEP, apply different recording approaches for quantifying regional displacements of THA to estimate air volume components. Comparisons have been made with the PNT, but the PNT only gives information about airflow, not regional amplitudes of the THA (Duranti et al. 2002; Clarenbach et al. 2005). Even among those technologies that record different regions of the THA, different recording approaches are used to quantify different anatomical sites, making direct comparisons more challenging. There is therefore a lack of well-standardised normative data for the differences in separate displacements of the RC and the AB to the total THA motion between current recording methods.

Since the RIP and the SLP use different anatomical sites to quantify THA movements, some discrepancies in their measurements were expected. The RIP records changes in motion of the

cross-sectional area of the RC and the AB from two narrow bands around the whole THA circumference. On the other hand, the SLP quantifies motion changes of the whole surface of the THA, but only anteriorly. The RIP band corresponding to the RC motion is standardised to be placed at the level of 4^{th}-6^{th} ribs, but this restricts the quantification of the circumferential RC motion only to these specific anatomical area cover by the band (Konno and Mead 1967; Tobin 1992; Wolf and Arnold 2005). The RIP band for quantifying the AB motion is placed at the level of the umbilicus and may not capture the area of the abdomen, which is most likely to move when the diaphragm activates during respiration (Aliverti et al. 2001). The area most likely to move during respiration is the costal portion from the end of xiphoid process to the upper margins of the lower rib pairs (Mead and Loring 1982; Pettiaux et al. 1997; Romagnoli et al. 2008; Kaneko and Horie 2012). On the other hand, the SLP quantifies regional displacements of the THA between the clavicles and the umbilicus, but only anteriorly. Based on the above equipment differences regarding their recording approaches, larger breath sizes (reflected in greater amplitudes of RC_{amp} and AB_{amp}) were more likely to show greater discrepancies between the RIP and the SLP.

In addition to this, both recording methods measured an average increase in RC_{amp} after exercise supporting the SLP's ability to detect changes in THA movements, as previously reported by Elshafie et al. (2016). It is worth noting that the validation study presented here showed that changes in the RC_{amp} and the AB_{amp} measured by the RIP after exercise were almost double from those estimated by the SLP. This may be not only due to the different recording approaches used by the comparable methods, but also due to the changes occurring in breathing kinematics between resting breathing and after exercise. Studies characterising the kinematics of THA movements in healthy adults at rest have showed that the diaphragm contracts during inspiration, moving downward into the abdominal area cavity causing its expansion (Kenyon et al. 1985; Chihara et al. 1996). The lower ribs (8^{th}-12^{th}) tend to move upward, forward and outward to increase the volume of the thoracic cavity as reflected by expansion of the RC (De Troyer et al. 2009; De Troyer et al. 2011).

During exercise and immediately after exercise, increased ventilatory demands are responsible for an increased neural drive to the respiratory muscles. This, in turn, results in an increased mechanical power generated by the respiratory muscles (Aliverti et al. 1997). This requires the recruitment of accessory respiratory muscles, which are mainly found in the upper thoracic area, inducing a greater RC expansion. This is characterised by anteroposterior, lateral and transverse movements of this area in association with greater inhaled air volumes (Aliverti 2016). In this validation study, respiratory muscle function was not monitored to confirm the above behaviours in breathing kinematics during recovery time after exercise, but the RR was found to be

significantly increased immediately after exercise showing increased ventilatory demands within participants after exercise.

Since the SLP uses a grid pattern to monitor changes only in the anterior surface of THA movements, it is not likely to detect any lateral movement of the RC. Later movements of the RC are more likely to be present during faster resting breathing rates in large air volumes (Aliverti 2016). In contrast, the RIP does detect circumferential changes of the RC and the AB, even though this is restricted to a small part of these areas (Grossman et al. 2010; Cabiddu et al. 2016). Therefore, there is potential for larger values of RC_{amp} and AB_{amp} to be obtained by the RIP compared to the SLP, especially during larger breath sizes. This may further raise concerns about the ability of SLP to accurately measure air volume components in the future, since this technology records only one dimension of THA movements.

To date, it is not clear whether the identified differences between the RIP and the SLP for the amplitudes of regional displacements of THA can be considered clinically meaningful due to a lack of normative standardised data. However, the two devices were found to agree when measuring the RC_{amp}/AB_{amp} during both respiratory phases, both at rest and after exercise. Good breath-by-breath agreement was found, without within-individual variability violating their measurement agreement. The SLP was considered as a means to quantify objectively the proportionality of motion of these two compartments of THA irrespective of the actual magnitude of the RC and AB displacements over a variety of breath sizes obtained during resting breathing or during rapid breathing.

5.4.2 The use of the Structured Light Plethysmography as a valid monitoring tool in this research

The SLP is a relatively new contactless method for recording the THA movements and extrapolating various breathing pattern components. It is portable and there is no requirement for complex calibration procedures, as a result it has been reported to be suitable for use outside a laboratory environment (Elshafie et al. 2016). The SLP's software can provide direct numerical data of breathing pattern components, giving instant quantification of them with no need for signal processing techniques after data acquisition. The validity of the SLP's direct numerical data generation was beyond the scope of the present study, so raw data were extracted and examined as previously described. Subsequent studies of this research presented in this thesis employed the same procedure. This was not only to maintain consistency across the studies included in this research, but also to obtain estimates of parameters associated with THA movement, such as the RC_{amp}/AB_{amp}, as validated in the present study and they are not provided automatically by the SLP.

The main advantage of the SLP is that it does not require direct contact with patients through the use of bands, reflective markers, facemasks, mouthpieces or nose clips requiring minimal individuals' cooperation (De Boer et al. 2010; Motamedi-Fakhr et al. 2017b). To date, the SLP has been shown to record the natural variability of timing parameters without inducing instrumental changes or changes due to individuals' awareness of breathing measurement (Nierat et al. 2017). Although the RIP has been also reported not to induce instrumental changes in breathing pattern measurements (Han et al. 1997), the SLP was deemed to be the preferred device in this research, partly because of its fully contactless nature.

In addition, since SLP was found to be a valid and responsive monitoring method for measuring breathing pattern components of interest of this research, it was selected as suitable form of technology for quantifying these breathing pattern components in the subsequent studies of this research. Monitoring the anterior surface of the whole THA was found to be a valid recording method for providing estimates of timing parameters and the RC_{amp}/AB_{amp} during both respiratory phases at rest breathing and in the presence of high breathing rates, as might be found in patients with asthma in the subsequent studies of this research. Nevertheless, the SLP should be generally used with caution if it is used for estimating direct measurements of the individual measures of the RC_{amp} and the AB_{amp}. The discrepancies between the two methods for measuring these parameters over greater amplitudes raises concerns about its suitability for measuring air volume parameters in the future after determining appropriate calibration procedures.

5.4.3 Limitations of the validation study

The primary interest of this study was to assess the measurement accuracy of the SLP in comparison to the RIP, irrespective of the underlying breathing patterns of studied individuals. However, the majority of the study's sample was healthy adults. A study by Motamedi-Fakhr et al. (2017b) included a small number of patients with acute respiratory problems such as COPD (n=6) and asthma (n=4). The authors reported that the SLP could measure accurately timing parameters in these patients as compared to the PNT. This can make the SLP suitable for breathing pattern measurements in individuals with potentially altered breathing patterns from those of healthy individuals as the present validation mainly involved. However, the SLP's ability to measure accurately both timing parameters and the RC_{amp}/AB_{amp} during both respiratory phases in a variety of breath sizes, as may occur within individuals of different respiratory health status, has been confirmed by this validation study.

This validation study examined the SLP's accuracy in a relatively young population with normal BMI even though recruitment of a heterogeneous sample was attempted. This may raise concerns

about the SLP's performance in other groups of people such as those with different demographic data (elderly or obese adults). However, at present, there is no a reference standard device for having been standardised to measure breathing patterns in obese people. Both the RIP and the OPE have been reported to underestimate breathing pattern measurements, especially air volume components and the regional contributions to the THA movements, in obese individuals (Boudarham et al. 2013; Retory et al. 2017).

In contrast, individuals with a greater range of age (min 6 years, max 78 years) were involved in the study by Motamedi-Fakhr et al. (2017b). The authors did not report any inaccuracy in the SLP's measurements due to the participants' age. Nevertheless, the authors did not report the BMI among the different study groups (healthy, patients with COPD or asthma) and this still raises the need for future work. Another limitation of the validation study is that breathing pattern components were measured only in the sitting position, partly because it is one of the common postures for evaluating respiratory system in routine clinical practice and because of the type of the size of the SLP, which was available to the researcher. To the best of the researcher's knowledge, the SLP has not been validated in other postures compared to another recording method, apart from the sitting posture. As a result the SLP should be used with caution in other postures, such as standing or supine, till the further examination of its accuracy within these postures.

In addition, the reliability of the SLP was not specifically examined within this study as its primary aim was to test the criterion-validity of the SLP under different recording conditions. However, recent published evidence has reported that SLP can provide reliable measurements, based on the lack of differences in the agreement between the PNT and the SLP during two consecutive resting breathing sessions (Motamedi-Fakhr et al. 2017b).

5.5 Summary of the validation study

The SLP was found to be a valid technology for measuring quantifiable breathing pattern components in healthy adults at rest and immediately after submaximal exercise (increased breathing rates). The SLP was found to measure timing components and the proportionality of the RC_{amp} to AB_{amp} ($RC_{amp}/_{amp}$) in agreement with the RIP at rest and after exercise, without within-individual variability of breathing patterns changing their between measurement agreement. The responsiveness of the SLP was also concluded from the data of the validation study. The SLP was able to detect changes in timing parameters and the RC_{amp}/AB_{amp} (during both respiratory phases) after the submaximal exercise. Based on these findings, the SLP was deemed a suitable form of technology to be used for measuring the quantifiable breathing pattern components of interest of

this research. To be reminded, this research aimed to determine their potential use as a physiological marker in asthma management.

Chapter 6 The association between quantifiable breathing pattern components and asthma control: a correlational study

After determining a suitable form of technology for measuring quantifiable breathing pattern components of interest of this research, the next phase was to primary look at their use in relation to asthma control and secondary their associations with other asthma-related outcomes used in asthma management. This is in line with gaps of knowledge identified in this research area as discussed in Chapter 3 (sections 3.4, 3.4.1, 3.5 and 3.6). The present chapter provides the description of the correlational study of this research. An individual discussion of the study's findings and limitations are also provided at the end of the same chapter.

6.1 Aims and objectives of the correlational study

This study primary aimed to establish if specific components of breathing patterns were associated with asthma control on one occasion. So, the author explored whether the examined quantifiable breathing pattern components could predict asthma control. A post-hoc analysis was further performed to look at their ability to evaluate asthma control. A secondary aim of this study was to further examine whether the examined breathing pattern components could be used as a surrogate marker for other patient-related outcomes used in asthma management. This included the examination of the association between the examined breathing pattern components and clinical measurements of the DB, lung function measurements and asthma-related quality of life.

The examined quantifiable components of breathing patterns were a) timing parameters (RR and Ti/Te) and b) the proportion of RC motion to AB motion (RC_{amp}/AB_{amp}) during both respiratory phases as established to be measured by the SLP when compared to the RIP.

The objectives of this study were:

1) To collect the above breathing pattern data from adult patients with asthma. Absolute parameterised values of the RR (expressed as bpm), the Ti/Te and the RC_{amp}/AB_{amp} during both phases ($RC_{ampinsp}/AB_{ampinsp}$ and RC_{ampexp}/AB_{ampexp}) were measured. A definition of these parameters has been previously provided in chapter 5 (see section 5.2.6). A breath-by-breath analysis over time enabled the estimation of the within-individual variability of the above

breathing pattern components. This was determined by the coefficient of variation (CoV) expressed in a percentage (%).

2) To obtain data relating to perceived levels of asthma control, the presence of DB and the patient's quality of life. The tools used to collect data about these outcomes are provided in detail within the section 6.2.6.2.
3) To collect data regarding lung function measurements, such as $\%FEV_{1\ predicted}$, FEV_1/FVC and PEF. The tool used to collect this data is the same with that used in the validation study and presented in the section 6.2.6.4.

The theory behind this correlational study was that increased RR, and/or disproportional respiratory phases (characterised by a shift towards shorter Te than Ti) and/or a shift towards greater RC_{amp} over AB_{amp} could primary predict uncontrolled asthma, as measured in a single occasion. Also the above breathing components could be secondary used to predict the presence of DB, poor asthma-related quality of life and declined lung function.

6.1.1 Research question

The primary research question was: Can the above quantifiable components of breathing patterns (absolute measurements and/or within-individual variability) predict asthma control on one occasion?

Other secondary research questions to be answered by this study were:

1) Can the above quantifiable components of breathing patterns predict presence of the DB?
2) Can the above breathing components predict lung function measurements?
3) Can the above breathing components predict asthma-related quality of life?

6.2 Methods of the correlational study

The following sections present the methodology undertaken to meet the aims and the objectives of the correlational study presented in this chapter.

6.2.1 Study design

An observational cross-sectional study design involving a sample of adult patients with varying asthma control, was used to identify associations between specific breathing pattern components and asthma control along with other asthma-related outcomes used in asthma management. Associations between these variables were attempted to be established using two predictive models as presented in the section 6.2.9. Breathing patterns were recorded for 5 minutes within a

single recording session whose total duration was 30-40 minutes. Breathing patterns were recorded by SLP in the sitting position and during resting breathing as performed in the validation study.

6.2.2 Settings and ethical considerations

Willing patients with asthma who met the eligibility criteria of the study were invited to attend a single recording session within NIHR Southampton Clinical Research Facility (Welcome Trust) at University Hospital Southampton (UHS) NHS Foundation Trust. The study had initially been peer-reviewed and ethically approved by the School of Health Sciences, Faculty of Environmental and Life Sciences (ERGO II number: 27461.A1) prior to seeking for additional Health Research Authority (HRA) acceptance (see Appendix B). Additional ethical approval was obtained by responsible authorities, such as the London-Queen Square Research Ethics Committee (REC reference: 17/LO/1640) and the HRA (IRAS project ID: 230295) in September and October 2017 respectively (see Appendix B). The final R&D approval from the UHS was obtained in February 2018 (see Appendix B).

6.2.3 Participants' eligibility criteria

The eligibility of the study participants was based on pre-determined inclusion and exclusion criteria. The following table provides a summary of the study's eligibility criteria. Breathing pattern data were obtained from a heterogeneous sample of asthma patients in terms of asthma phenotype and other demographic data such as age, gender and BMI. Due to asthma heterogeneity, there are different asthma phenotypes, but only inflammatory markers, such as FeNO or eosinophilic counts, have been reported to be dependent on the asthma phenotypes (Michils et al. 2008). Therefore, adult patients (aged 18 and over) with an asthma diagnosis (as previously determined by a clinical practitioner) and different asthma phenotypes (atopic and non-atopic asthma) were eligible for this study. Eligible individuals had to be receiving asthma medication (from Step 2 to Step 5 asthma treatment) according to the GINA guidelines (2017) or had to be taken short acting $beta_2$ agonists (SABA) during the last 2 months prior to the data collection, due to presence of acute asthma symptoms.

Patients who self-reported any other chronic respiratory problem, such as COPD, were not eligible for this study. Additionally, individuals who had any chest infection, or upper respiratory tract infection on the day of data collection, or during the past week prior to data collection were not eligible for this study. This was not only because of any potential effect of these respiratory problems on breathing pattern measurements, but also because of the potential impact of the

above respiratory problems on patients' perception about their actual asthma control and their health status. Patients with ACQ scores between 0.75 and 1.50 were not studied. This was because the ACQ was being used as a binary outcome for the needs of this correlational study as discussed in the sections 6.2.4, 6.2.6. Finally, individuals who were not willing to sign a written consent form (see Appendix B) were not eligible for this study.

Table 6-1: Summary of participants' eligibility criteria for the correlation study

Inclusion criteria	Exclusion criteria
Adults aged 18 or over	Presence of other co-existing chronic respiratory problems such as COPD
Diagnosis of asthma as made by a clinical practitioner	
Patients who were on STEP 2, STEP 3, STEP 4 or STEP 5 asthma treatment according to GINA guidelines (2017)	Presence of chest infection, cold or acute allergy on the day of breathing pattern recording or during the past week prior to breathing pattern recording
Individuals who may have used SABA medication during the past 2 months	Anyone who was unwilling to sign a written consent form

6.2.4 The estimation of the sample size of the correlational study

Identifying associations between a binary or continuous outcome (known also as a dependent variable) via the use of predictors (known also as independent variables), requires a larger sample size, than interventional studies (Maxwell 2000; Kelley and Maxwell 2003). An estimation of a minimum adequate sample size was required to meet the principles underlying the different types of regression analyses that were applied in this correlational study. Both linear and logistic regression analyses were planned to be performed, due to the presence of different types of examined outcome variables (continuous and categorical) as further discussed in the section 6.2.9. Balanced against this were the practicalities of recruiting a very large sample of patients within the available timeframe of this research programme. This led to a pragmatic choice when estimating a minimum sample size based on rules of thumb for different regression analyses.

There are several rules of thumb, which can be considered as inconclusive power calculations for meaningful minimum sample sizes in correlational studies (VanVoorhis and Morgan 2007). A general vague rule of thumb suggests that a sample size of at least 50 individuals can be considered as an adequate sample for applying simple linear regression analysis (VanVoorhis and Morgan 2007). However, this was deemed inconclusive and not applicable in this correlational study, as different regression analyses were performed.

Harris (1985) suggested a mathematical equation to be used as a simple rule of thumb for both simple and multiple linear regression analysis. The mathematical equation was N >50+K; where N is the required sample size and K is the number of predictors. Harris (1985) recommends that the number of participants needs to be greater than the number of predictors by at least 50 observations when the predictors are ≤5. This rule of thumb has been criticised due to its inability to meet all the different criteria that are required to be tested within a multiple linear or logistic regression analysis. These are how well the regression model fits the collected data (R^2) and the contribution of beta coefficients of predictors to the model.

Green (1991) suggested two different methods for estimating a minimum sample size for multiple linear regression analysis. A sample size of N >50+8K was suggested to test sizes of the R^2, whereas testing the contribution of predictors requires a sample size of N> 104+K. In the correlational study, both R^2 and beta coefficients of two different 3-predictor regression models were evaluated. Consequently, a sample of 107 individuals was considered to be a reasonable minimum sample size for the needs of multiple linear regression analysis applied in the study. On the other hand, it was recognised by the author that this sample size would not be sufficient for the needs of the multiple binary logistic regression applied to examine the association between the examined breathing pattern components and the primary outcome variable (asthma control).

The rules of thumb approach for logistic regression analysis requires the absence of an over-fitted model, characterised by more predictors than the number of observations for each category of an examined outcome (Stoltzfus 2011). This is likely to provide large standard errors of beta coefficients and a wide range of 95%CI of odds ratio. In general, a rule of thumb of 20 has been recommended to estimate a sufficient sample size for applying multiple binary logistic regression (Peduzzi et al. 1996). This recommends that there should not be fewer than 20 observations of each category of a binary outcome for each predictor applied in the model.

In this study, the primary variable of interest was asthma control and it was used as a binary variable (well-controlled and uncontrolled asthma) using a minimum number of 3 predictors for each regression model (absolute measurements or %CoV of the examined breathing pattern components). As a result, a minimum sample of 120 patients with asthma was determined as a pragmatic sample size. A sample size of 200 individuals was pre-determined as a maximum total sample size, to allow potential subsequent analysis using more predictors in each model and further examining associations in large subgroups determined by the gender or the asthma severity, according to the collected data. This maximum sample of 200 individuals was estimated by any potential use of 2 more predictors in the models for the needs of multiple binary logistic regression.

6.2.5 Patients' recruitment process

The final number of enrolled participants in this study was 122 patients with different asthma severity. After gaining appropriate permission, posters (see Appendix B) were displayed on notice boards in different Faculties of the University of Southampton. The posters were also displayed on notice boards at the UHS. Awareness of the study was increased through articles in newspapers, such as the Southern Daily Echo and Daily Mail. Anyone who was interested in taking part in the study was advised to contact with the researcher via email address. The eligibility criteria were initially checked via a screening sheet (see Appendix B) and then a convenient appointment for data collection was arranged.

Patients with more severe asthma were also recruited from a difficult-to-treat outpatient asthma clinic taking place one or two times per week at the UHS. New patients attending the outpatient clinic and those who had been previously enrolled in an ongoing severe asthma cohort study (known as WATCH study) and had a routine clinical appointment, were given the study's information pack (see Appendix B). The WATCH study was a longitudinal observational study aiming to identify clinical characteristics of asthma phenotypes in a severe asthma cohort. The study's information pack consisted of an invitation letter and a participant information sheet (PIS) (see Appendix B), through which individuals were able to be fully informed about the study. If the patients were willing to take part in the study and met the eligibility criteria, an appointment for data collection was made. The appointment for data collection was either on the same day after their routine clinical appointment, or another day according to the participants' convenience and availability. The following flowchart summarises the recruitment procedure. Eighty-one patients were recruited from the difficult-to-treat asthma outpatient clinic, whereas 41 participants were recruited via the posters and advertisements in the press.

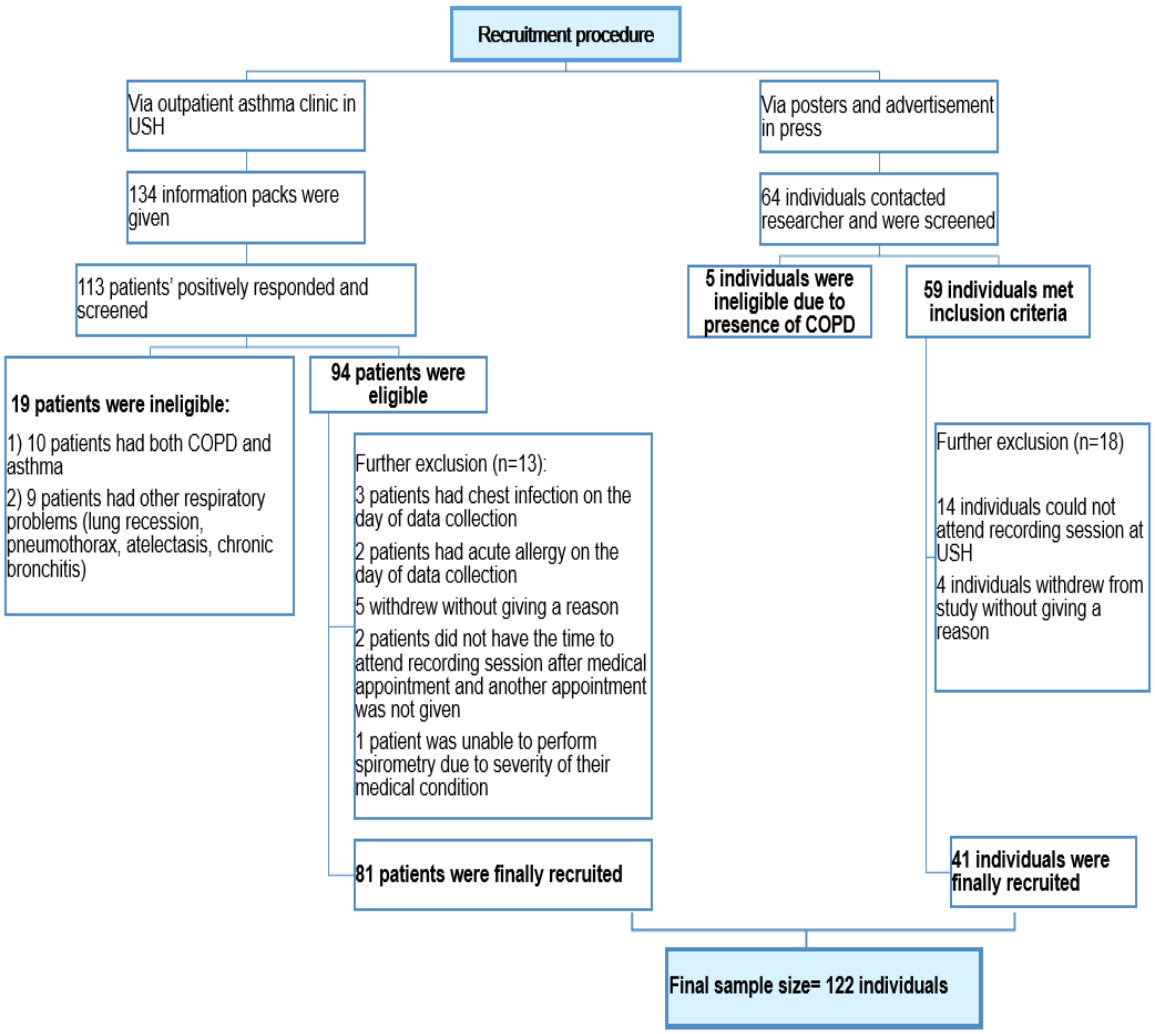


Figure 6-1: A flowchart summarising the recruitment process of the correlational study

6.2.6 The equipment used in the correlational study for the data collection

6.2.6.1 Demographic data and data regarding patients' medication usage

Upon participants' arrival for data collection, written consent was given via a consent form (see Appendix B). A case report form (CRF) (see Appendix B) was completed by the researcher to obtain patients' demographic data. Demographic data involved information regarding the patients' age, gender, height and weight (as measured by a calibrated scale), their BMI (expressed in kg/m^2), their self-reporting age of asthma diagnosis and their asthma phenotype as documented by the participants having had a past positive allergy skin test.

The controller and rescue medication usage was also reported on the CRF on the day of data collection. The patients' controller medication was used to determine the participants' asthma severity in accordance with the GINA guidelines for adults' asthma management (2017) (see Chapter 2, section 2.3). The individuals on STEP 2 treatment (daily use of low dose of ICS and SABA as needed) were considered as having mild asthma. The participants on STEP 3 (daily use of

low dose of ICS plus the LABA use and the SABA as needed), STEP 4 (daily use of low or medium doses of ICS, the LABA use, or use of tiotropium and SABA as needed) and STEP 5 (daily use of medium or high doses of ICS, or tiotropium use, or low dose of oral corticosteroids and SABA as needed) were determined as having moderate-to-severe asthma.

6.2.6.2 The use of questionnaires to collect the examined asthma-related outcomes

Validated questionnaires were used to collect data regarding 1) asthma control, 2) presence of the DB, 3) the emotional status (anxiety and depression) and 4) the asthma-related quality of life.

The Asthma Control Questionnaire (ACQ)

As mentioned in Chapter 2 (see section 2.5), there are several valid questionnaires to quantify asthma control, and the $ACQ_{7\text{-item}}$ was chosen to measure perceived asthma control in this study. A description of $ACQ_{7\text{-item}}$ was previously provided in section 2.5.1. This questionnaire includes an item regarding $\%FEV_{1predicted}$ that other questionnaires omit, such as the ACT. The inclusion of this physiological marker is considered to be an important parameter for the quantification of asthma control (Ko et al. 2012). Although shorter versions of this questionnaire have also been found to be valid (Juniper et al. 2006), it has been suggested that the $ACQ_{7\text{-item}}$ should be used to quantify asthma control when lung function measurements are available (GINA 2017).

As mentioned previously, the $ACQ_{7\text{-itemm}}$ cut-off points are standardised for distinguishing different levels of asthma control, such as well-controlled and uncontrolled asthma (Alzahrani and Becker 2016). If the $ACQ_{7\text{-item}}$ is used to identify patients with well controlled asthma (minimal risk of being uncontrolled), a judicious cut off point is <0.75 with 85% chance of the patients' asthma being genuinely well controlled (Juniper et al. 2006). On the other hand, a cut-off point ≥1.50 shows not-well controlled asthma with 88% chances of the asthma being genuinely uncontrolled (Juniper et al. 2006). The area between these scores can be characterised as a "grey zone" of the instrument and patients with scores between the above standardised cut-off points being considered as having partially controlled asthma (Juniper et al. 1999). In this study, the ACQ was used as a binary variable based on the sample size of this study and it was used to identify well-controlled or uncontrolled asthma.

The Nijmegen Questionnaire (NQ)

The NQ was used to determine a possible presence of DB in the participants enrolled in this study. It is the current monitoring method used in clinical practice to assess for DB, even though there is ambiguity about its ability to detect genuinely altered breathing patterns (Li Ogilvie and Kersten 2015). As mentioned in chapter 3 (see section 3.4), the NQ is used to evaluate a range of

respiratory and non-respiratory symptoms (Boulding et al. 2016). A description of this questionnaire and several cut-off points for evaluating the presence of DB were previously provided in section 3.4. In clinical practice, a NQ score >23 is conventionally considered to indicate the presence of DB (Boulding et al. 2016). However, in patients with asthma, lower scores than 23 have been reported not to exclude the possibility of presence of DB. Grammatopoulou et al. (2014) suggested a cut-off point >17 for indicating DB in people with mild-to-moderate asthma, with sensitivity and specificity being 92.7% and 91.6% respectively.

In this study, the NQ was used as a binary variable. Since there is debate about the NQ cut-off points for monitoring a presence of DB in asthma, the absence of DB was set as a NQ score of 10 or below in this study. This was done to give certainty that the DB was not present in those individuals with these scores. This cut-off point was lower than those suggested in some previous studies by Grammatopoulou et al. (2014) and Boulding et al. (2016). The selected NQ cut-off score was in line with the original development and validation study of the NQ by Van Dixhoorn and Duivenvoorden (1985). The authors initially validated this cut-off point for describing the absence of hyperventilation, with points between 10 and 20 showing mild hyperventilation and points above 20 showing presence of hyperventilation.

The Hospital Anxiety and Depression Scale (HADS)

The HADS questionnaire was used as a validated instrument for monitoring the patients' emotional arousal. It was developed by Zigmond and Snaith (1983) and it is a 14-item scale with 7 items being related to anxiety and the rest of them being associated with signs of depression. A range of scores from 0 to 3 can be obtained for each item of the questionnaire's sub-domains. As a result, a total score from 0 to 21 can be obtained for each domain. In the literature, the cut-off points of the HADS questionnaire have been standardised with HADS scores >8 indicating signs of either anxiety or depression (Bjelland et al. 2002). This questionnaire was mainly used to characterise the emotional status of studied patients, as there is known to be high prevalence of anxiety in patients with asthma, especially in those with uncontrolled asthma (Ritz et al. 2013). In breathing pattern literature, it has been also suggested that emotional arousal may have an impact on specific quantifiable components of breathing patterns such as the RR and the Te (Masaoka and Homma 1999; Homma and Masaoka 2008). Therefore, monitoring emotional arousal of studied patients could help to understand any potential unexplained variance in the examined breathing pattern measurements in relation to asthma control.

The Mini-Asthma Quality of Life Questionnaire (mini-AQLQ)

The mini-AQLQ is another asthma specific instrument, which was used to evaluate patients' quality of life in the study. It was developed by Juniper et al. (1999) in response to a need for a shorter version of the original 32-item AQLQ. The mini-AQLQ has been found as a valid and reliable questionnaire compared to its original version (Juniper et al. 1999). It consists of 15 items related to 4 different domains, such as the asthma symptoms, the activity limitations, the environmental factors and the emotional arousal. The patients are required to recall their experiences during the past 2 weeks and rate the frequency of the items given in the questionnaire. Scores between 1 (all the time) and 7 (none of the time) can be obtained for each item and a mean score can be obtained by dividing the total score with the number of items included in the questionnaire.

High mini-AQLQ scores indicate better quality of life compared to lower scores (Juniper et al. 1999). However, there is lack of well-standardised cut-off points for discriminating patients with good quality of life versus poor quality of life. An indicative cut-off point of this questionnaire has been reported in a predictive validation study by Schatz et al. (2012), who found that a mini-AQLQ cut-off point <4.7 was a judicious threshold for having high risk of future asthma exacerbations. Due to a lack of a standardised cut-off point for categorising patients with good quality of life from those with poor quality of life, in accordance with asthma control, the mini-AQLQ was treated as a continuous variable for the needs of the statistical analysis as presented in the section 6.2.9.4.

6.2.6.3 Breathing pattern measurements

The examined quantifiable components of breathing patterns were a) the RR and the Ti/Te and b) the RC_{amp}/AB_{amp} during both respiratory phases. The within-individual variability of these components was also obtained via their continuous measurement for 5 minutes using the SLP (Thora-3Di^{TM}; Pneumacare Ltd, Cambridge, UK) as a suitable form of recording technology. The examined breathing components were recorded in the sitting position during spontaneous resting breathing. According to the literature and the SLP validation study included in this PhD work, the SLP was considered to be a valid monitoring method for measuring these breathing components during resting breathing. A detailed description of the SLP has been previously provided in sections 4.3.2 and 5.2.7. The breathing pattern recording process was the same as followed in the validation study of this research.

6.2.6.4 Lung function measurements

In addition to the measurements regarding the patient-related outcomes and breathing pattern data, a portable calibrated spirometer (Vitalograph, Alpha) was used to obtain lung function

measurements and their predicted values were estimated according to the participants' gender, age, height and ethnicity. The same calibrated spirometer was used in the validation study. The participants performed a forced vital capacity manoeuvre requiring participants to take a maximum deep breath and then form a tight seal around the disposable mouthpiece. After this, they exhaled with force as fast as possible until they felt their lungs to be fully empty. The participants' forced expiration lasted for a minimum of 6 seconds. This was performed three times with 1-2 minute breaks taking place between each attempt according to the participants' needs. Performing lung function tests was in line with guidelines for implementing optimal Spirometry as suggested by Miller et al. (2005).

6.2.7 Data collection procedure

The figure below presents the sequence of events during the data collection procedure of this study. The researcher acquired demographic data, and information about the patients' asthma and the medication usage were self-reported by the patients. Then the questionnaires were completed by the participants, taking maximum 10-15 minutes. After this, breathing pattern recordings took place using the SLP with the participants in a sitting position. A straight high-back chair with supportive arms was used. The participants were asked to wear a close-fitting white T-shirt. This was to enable the accurate projection of the SLP's grid pattern as described in the validation study of the SLP (see section 5.2.8). The participants were then given 3-4 minutes to feel comfortable and adjust to the experimental environment.

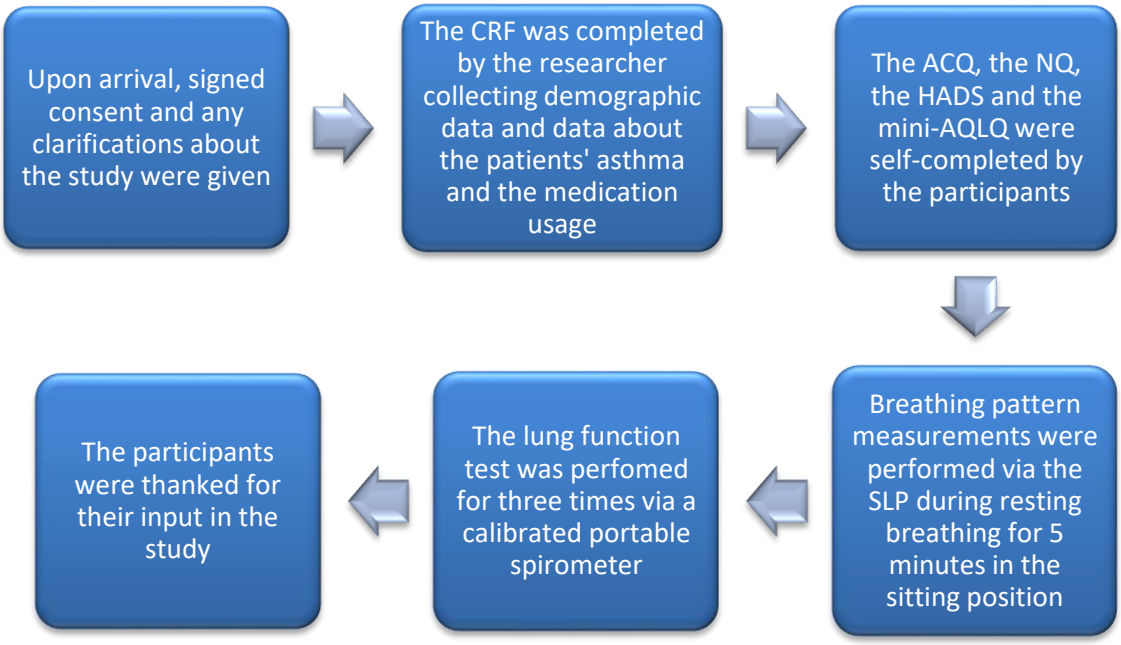


Figure 6-2: The sequence of the events during data collection of the correlational study

The participants were advised to stay still and quiet during the whole recording procedure to avoid any baseline shifts on the SLP's signal, as illustrated by an orange line on the attached computer screen. The individuals were advised to feel free to cough if needed. This was to allow the recording of natural behaviour of spontaneous breathing avoiding modifications of breathing from the patients. When a participant coughed or moved, the time was noted by the researcher to enable the removal of those respiratory cycles during extraction of breathing pattern data as presented in the next section (6.2.8).

When participants felt comfortable and were ready to be recorded, they were falsely informed that the recording was starting. The actual recording time started 1 minute after the initial notification. This was to further eliminate, as much as possible, any potential impact of patients' awareness of breathing pattern measurement on the natural behaviour of their breathing. Studies regarding awareness of breathing pattern measurements via the use of invasive monitoring methods, such as the PNT, have suggested that one minute is the relative time needed for individuals to adjust to an invasive recording device (Han et al. 1997).

After breathing pattern measurements for 5 minutes in total, the lung function test was performed via a calibrated portable spirometer. Once the quality of any collected data had been assessed, patients were thanked for their input in the study and were free to leave the laboratory. Good quality of data was obtained at the first attempt, but 13 patients coughed within the 5-minute recording period. The researcher noted the time and removed those breath cycles during breathing pattern data extraction in the Matlab software as presented in the following section.

6.2.8 Extraction of breathing pattern data

Breathing pattern data was initially saved in the SLP's CSV files and then inserted in the Matlab software on the researcher's personal computer. The data were saved as Matlab.mat file with an individual code for each participant. Parameterised values (mean values and sd) of the examined breathing components were extracted using the Matlab software (same version as used in the validation study) after performing a breath-by-breath analysis. Obtaining mean values and sd for each examined breathing component allowed the estimation of Coefficient of Variation (CoV) (as calculated by sd/mean value x 100 and expressed in %). After analysing the SLP signals in the Matlab software as performed in the validation study (see section 5.2.10), values of the examined breathing components were saved in Excel files.

One difference in the procedure for breathing data extraction between the validation study and the correlational study was the omission of the signal alignment process. This was only required for the validation study. However, the same automatic peak detection algorithm was used to

identify local minima and maxima for each detected breath cycle throughout the 5-minute recording period. Despite the use of the automatic peak detection algorithm, the researcher further edited signals from 13 patients who had coughed during their recording session. This was noted by the researcher during the actual recording as not illustrating real breath cycles, due to the presence of baseline shifts on the SLP output signal. Removal of these cycles was performed manually by removing troughs and peaks on the received signals. An example of a 'not real' breath cycle due to a baseline shift which led to its removal is illustrated below. A summary of the number of deleted breath cycles among the 13 patients is provided in the Appendix C.

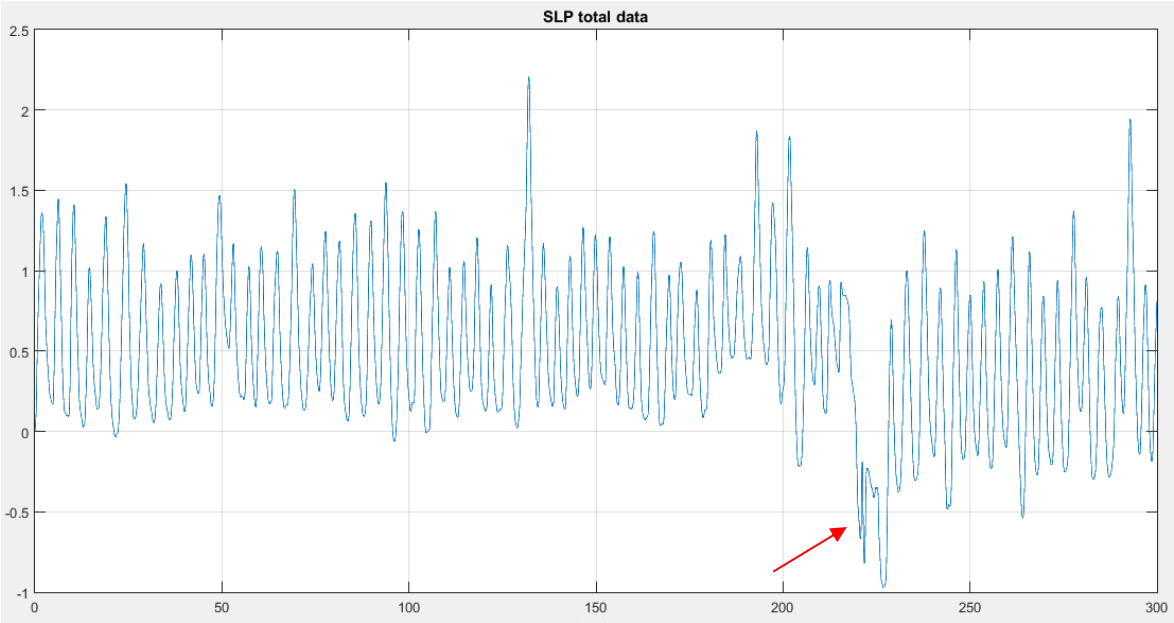


Figure 6-3: An example of the SLP sum output time trace used for breathing pattern data extraction including a 'not real' breath cycle (indicated by the red row).

6.2.9 The statistical plan of the correlational study

The following sections present the statistical analysis performed in the correlational study. The statistical analysis was performed using the latest available version of the SPSS (version 25).

6.2.9.1 Characterisation of the study sample

Descriptive statistics (mean values and sd) were used to summarise the patients' demographic data when entered into SPSS as continuous variables. Data regarding a) the gender, b) the asthma severity, c) the asthma phenotype and d) the emotional arousal, were summarised to characterise the study's sample. Sample mean (plus sd, 95%CI and min-max) of both examined breathing components and lung function measurements were estimated.

6.2.9.2 The statistical analysis of the primary outcome variable - asthma control

6.2.9.2.1 Characterisation of the groups with varying asthma control

Allocation of the participants into two groups with different levels of asthma control (well controlled and uncontrolled), was performed according to the pre-determined $ACQ_{7\text{-item}}$ cut-off points (see section 6.2.6.2). Group median (m), minimum and maximum values for each examined breathing component were estimated. Mean values of lung function measurements and other asthma-related outcomes (such as the mini-AQLQ and the NQ) were calculated between groups.

Comparisons in the examined breathing pattern components between asthma groups were sought using a non-parametric independent t-test known as Mann-Whitney U test. The selection of this test was determined after checking normality and homogeneity of variance of breathing data within groups. Normality of data was checked by Kolmogorov-Smirnov test (SK test) and homogeneity of variance was tested using Leven's test (F test). Only the Ti/Te and the $\%CoV_{RCampinsp/ABampinsp}$ were found to be normally distributed ($p>0.05$), but these parameters did not meet the assumption of homogeneity of variance ($p<0.05$). On the other hand, the RR and the $RC_{ampinsp}/AB_{ampinsp}$ were normally distributed but they were not homogeneous among groups. Neither normal distribution nor homogeneity within groups were obtained for the rest of the examined breathing components.

The Mann-Whitney U test was used to test the null hypothesis of no differences (same medians) in each examined breathing component between groups. The threshold for statistical significance was chosen to be 95% with significant results initially being considered when the $p<0.05$. However, a Bonferroni correction was applied and a final significance level re-set at 99% ($p<0.01$), due to use of multiple independent t-tests.

6.2.9.2.2 A multiple logistic regression analysis for the asthma control

To meet the primary aim of this study, multiple binary logistic regression analysis was performed. This was to examine whether absolute measurements or the %CoV of the RR, the Ti/Te and the RC_{amp}/AB_{amp} (during both respiratory phases) could predict uncontrolled asthma. Therefore, two different 3-predictor regression models were fitted to the collected data. Regression model 1 included average values of the RR, Ti/Te and $RC_{ampinsp}/AB_{ampinsp}$ (or RC_{ampexp}/AB_{ampexp}) and the predictors of regression model 2 were the $\%CoV_{RR}$, the $\%CoV_{Ti/Te}$ and the $\%CoV_{RCampinsp/ABampinsp}$ (or $\%CoV_{RCampexp/ABampexp}$). The maximum number of predictors for each regression model was based on the total sample of the study as justified in section 6.2.4.

The assumption of no perfect collinearity states that there is no strong association among the predictors (independent variables) within a regression model (Field 2009, p 223). No perfect multicollinearity between predictors of each model was checked using collinearity diagnostics, such as the Variance Inflation Factor (VIF) and the tolerance values. Menard (1995) suggests that a tolerance value less than 0.1 can indicate violation of the assumption of multicollinearity. Myers (1990) also stated that a VIF value >10 can be a cause for concern. These values were used to evaluate multicollinearity between the predictors of each model included in this study.

The multiple binary logistic regression analysis was performed using the forced entry method. The predictors of each model were forced simultaneously into the models without the researcher making any decision about their order. Other methods such as stepwise methods (forward or backward) were not deemed appropriate. This was because this study was conducted for theory testing rather than aimed at exploratory model building, where stepwise methods are more appropriate (Field 2009, p 212). Also, it has been supported that stepwise techniques can be influenced by random variation in the collected data and so seldom give replicable results if the model is retested (Menard 1995).

To assess the regression models of the study, the log-likelihood statistic (-2LL), the Cox and Snell R^2, the beta coefficients of predictors and the odds ratio (Exp(B)) were checked. Both -2LL and R^2 were used to assess how well the models fitted the collected data indicating how much unexplained information was left after fitting the models (Field 2009, p 284). In general, large values of -2LL show poor fitting regression models. The larger the value of -2LL, the more unexplained observations there are. Regarding values of the R^2, it can take values between 0 (bad predictors) and 1 (perfect predictors) (Field 2009, p 266). In comparison to -2LL, the R^2 was expressed in a percentage showing the the variation in the outcome that could be explained by the multiple use of the specific predictors of the study.

The contribution of each predictor to each model was additionally checked via the Wald statistic test. This was used to test the null hypothesis that beta coefficient of each predictor in the models was not significantly different from zero. The chosen significant level was $p<0.05$. If the null hypothesis was rejected, it was meant that the predictor made a significant contribution to the prediction of the outcome. Additionally, the Exp(B) and 95%CI for Exp(B) were calculated with the Exp(B) being an indicator of the change in odds resulting from a unit change in the predictors. Values of Exp(B) >1 indicate that as the predictor increases the odds of the outcome occurring increase. Values of Exp(B) <1 show that as a predictor increases the odds of the outcome occurring decrease (Field 2009, p 271). The 95%CI for Exp(B) was a measurement of confidence about the direction of the relationship between the predictors and the outcome. When both

limits of 95%CI were >1, there could be confidence that the direction of the relationship between variables was true in the study's population (Field 2009, p 287).

In addition to the above, influential cases were looked at for each regression model. This was to understand whether models were biased by the presence of extreme cases. This was performed by looking standardised residuals and checking that no more than 5% of cases had values >2. Also unbiased regression models by extreme cases were considered those with no more than 1% of total cases with standardised residuals >2.5 (Field 2009, p 293). Influential cases were also determined by estimating the Cook's distance. Cases with values >1 were considered to be influential cases. Finally, the assumption of linearity between the predictors and the log of the outcome variable was checked to allow generalisations of the associations between the examined variables and the examined outcome variable.

6.2.9.2.3 Post-hoc analysis using diagnostic statistics after the identification of a significant regression model

When a regression model was identified to predict asthma control, a post-hoc analysis including diagnostic statistics was performed. This was to further look at the ability of the examined breathing components to classify patients with varying asthma control through suggesting cut-off values. Therefore, the specificity and sensitivity of the regression model were estimated using a classification table generated during the multiple logistic regression analysis in the SPSS.

Sensitivity of the model showed how well the predictors of the regression model could detect uncontrolled asthma, whereas the specificity showed how well the predictors identified patients with well-controlled asthma in the study's total sample. The sensitivity was estimated by TP/(TP+FN) and expressed in a percentage; where TP is the number of true positive observations and FN is the number of false negative observations (Thabane et al. 2013). Specificity was calculated by TN/(TN+FP) and expressed also in a percentage; where TN is the true negative observations and FP is the false positive observations. The Youden index (J) was used as an indicator for the regression model to be a good classifier. It was estimated as sensitivity+specificity-1 with values being between 0 and 1. Higher values indicate good separation (Youden 1950).

A receiver-operating characteristic (ROC) curve and the area under the curve (AUC) (plus 95%CI) were estimated. The ROC curve is a graphic plot, which was used to illustrate the ability of a regression model as a binary classifier of asthma control (Thabane et al. 2013). It was created by plotting the sensitivity against the false positive rate (known also as false alarm and calculated as 1-specificity) at various thresholds. Also, a ROC curve (plus AUC and 95%CI) for each predictor of a

regression model was used to provide cut-off points for each predictor as an individual classifier for asthma control.

6.2.9.2.4 A correlational analysis performed in subgroups

After identifying significant predictors of the outcome, applying regression analysis in subgroups would enable to cross-validate any significant result obtained from the total sample of the correlation study. Due to small sample sizes of the subgroups of this correlation study, regression analysis could not be performed. However, bivariate correlational analysis (Spearman Correlation Coefficient) between the examined breathing components and asthma control was performed in three subgroups to check consistency of the results. The subgroups of this study were the female group, the male group and the moderate-to-severe group.

6.2.9.3 The statistical analysis regarding associations between the examined breathing components and dysfunctional breathing

The NQ was used as a binary variable with NQ <10 being used to classify people with asthma as having no DB. The NQ scores between 10 and 17 were considered points in the grey zone of questionnaire with a lack of certainty about presence or absence of DB. However, since NQ was being used as a binary outcome in accordance with its original validation study by Van Dixhoorn and Duivenvoorden (1985), an NQ score ≥10 was used to show DB. Comparisons in the examined breathing components between groups were performed using the Mann-Whitney U test after checking normality and homogeneity of variance of breathing components. The same significance level was chosen as in section 6.2.9.2.1 after applying Bonferroni correction for multiple t-tests.

Predictions for the presence of the DB were made by using multiple binary logistic regression, using the forced entry method as described previously for the primary outcome variable of this correlational study (asthma control). Significant results were considered at $p<0.05$. Post-hoc analysis was also performed as described in the section 6.2.9.2.3.

6.2.9.4 The multiple linear regression analysis used for predictions of continuous outcome variables

The relationship of the examined breathing components with continuous outcomes was examined by using a multiple linear logistic regression. Continuous outcomes of this study were the lung function measurements and the mini-AQLQ scores. The same 3-predictor regression models were used as described for the primary outcome variable of the study (asthma control) (see section 6.2.9.2.2). Estimates used to evaluate the examined regression models included the R^2, the adjusted R^2, the F-ratio, and the both unstandardized and standardised beta coefficients of

predictors. A significant result was considered at $p<0.05$. Influential cases, normal distribution of residuals and assumption of independent errors (use of Durbin-Watson test) after applying the regression models were also checked and their results are provided in the Appendix C.

6.3 Results of the correlational study

The following sections provide the results of the correlational study. One of the examined breathing components was the RC_{amp}/AB_{amp} during both respiratory phases. Due to similar results regarding this specific breathing component, only the results of the $RC_{ampinsp}/AB_{ampinsp}$ and the $\%CoV_{RCampinsp/ABampins}$ are given in the following sections to avoid repetition. The full results about the RC_{ampexp}/AB_{ampexp} and the $\%CoV_{RCampexp/ABampexp}$ are provided in the Appendix C.

6.3.1 Descriptive data of the study's sample

In this study, 122 adults (75 females) with different asthma severity were studied. The patients' mean age (sd) was 44.75 years (15.98 years) with minimum and maximum age being 18 and 80 years respectively. The sample's mean BMI (sd) was 25.74 kg/m^2 (3.95 kg/m^2) and the minimum and maximum BMI were 18.26 and 38.29 kg/m^2 respectively. The 42% of the patients had normal BMI (18-25 kg/m^2), the 49% of them were overweight (BMI: 25-29 kg/m^2) and the 9% of them were obese (BMI≥30 kg/m^2).

Both atopic and non-atopic asthma phenotypes were studied with the 70% of the patients having atopic asthma. The sample's mean age (sd) of asthma diagnosis was 17.17 years (17.99 years). From those with atopic asthma, 68 out of 85 patients self-reported an asthma diagnosis when aged below 18 years, whereas 23 out of 37 patients with non-atopic asthma had an asthma diagnosis when aged over 18 years. Regarding asthma severity, 33 out of 122 patients had mild asthma (STEP 2), whereas the rest of the participants had moderate-to-severe asthma (STEP 3, 4 or 5) according to the GINA (2017).

The Table 6-2 summarises the study's sample mean values of the lung function measurements, the $ACQ_{7\text{-item}}$, the NQ and the mini-AQLQ scores. Only 28 out of 122 patients were found with fixed-airway obstruction (FEV_1/FVC <0.70). The Table 6-3 provides the study's sample mean values of the examined breathing components. Regarding the patients' emotional arousal, 25% and 14% of the studied patients had $HADS_{anxiety}$ >8 and $HADS_{depression}$ score >8 respectively with 6% of the total studied patients having both anxiety and depression.

Table 6-2: The lung function measurements and the questionnaires' scores obtained in the total sample of the correlational study (n=122)

Lung function measurements	**μ***	**sd***	**95%CI*** **Lower-upper**	**Min-Max***
$\%FEV_{1predicted}$	88.08	25.36	83.53-92.62	30.20-145.02
FEV_1/FVC	0.78	0.13	0.75-0.80	0.31-0.96
PEF (L/sec)	4.65	1.61	4.36-4.94	1.30-9.74
Questionnaires				
ACQ_{7item}*	1.57	1.32	1.33-1.80	0.00-5.71
NQ*	13.71	11.14	11.72-15.71	0-54
Mini-AQLQ*	5.29	1.42	5.04-5.55	1.40-7.00

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals; **Min-Max:** minimum and maximum values **ACQ:** Asthma control questionnaire; **NQ:** Nijmegen questionnaire; **Mini-AQLQ:** mini-Asthma Quality of Life Questionnaire

Table 6-3: The mean values of the examined breathing components obtained in the total sample of the correlational study (n=122)

Breathing components	**μ***	**sd***	**95%CI*** **Lower-upper**	**Min-Max***
RR (bpm)	15.41	4.23	14.65-16.17	7.09-32.02
Ti/Te	0.67	0.11	0.65-0.69	0.40-0.96
$RC_{ampinsp}/AB_{ampinsp}$	1.42	0.69	1.29-1.54	0.36-5.38
$\%CoV_{RR}$	9.65	6.18	8.55-10.76	0.00-29.71
$\%CoV_{Ti/Te}$	26.86	11.41	24.82-28.91	10.49-57.78
$\%CoV_{RCampinsp/ABampinsp}$	20.40	10.07	18.59-22.20	7.48-57.78

***** **μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals; **Min-Max:** minimum and maximum values

6.3.2 Results regarding asthma control

6.3.2.1 Descriptive data of the asthma control groups

The Table 6-4 provides the demographic data, the mean scores of the questionnaires and the lung function measurements between the well-controlled asthma group and the uncontrolled asthma group. From the total sample of this study, 59 patients had ACQ_{7item} <0.75 considering as having well-controlled asthma; 29 of whom had mild asthma, compared to 4 patients having mild asthma in the uncontrolled asthma group (ACQ_{7item} >1.50, n=63). There were similar number of male and female patients in each group and both groups had similar averaged BMI (see Table 6-4).

The uncontrolled asthma group's mean NQ score was higher than this in the well-controlled asthma group (see Table 6-4). The patients with uncontrolled asthma had lower mean mini-AQLQ score compared to the well-controlled asthma group. Although neither group had anxiety (mean $HADS_{anxiety}$ score <8), 7 patients with well-controlled asthma and 24 patients with uncontrolled asthma had $HADS_{anxiety}$ scores of >8. Similarly, neither group had depression (mean $HADS_{depression}$ score <8), but 2 patients with well-controlled asthma and 15 patients with uncontrolled asthma had $HADS_{depression}$ scores of >8. The well-controlled asthma group had higher average lung function measurements than the uncontrolled asthma group (see Table 6-4). Only 6 patients with well-controlled asthma and 22 patients with uncontrolled asthma had FEV_1/FVC <0.70 indicating presence of fixed-airway obstruction within these participants.

Table 6-4: Summary of the demographic data, the mean scores of questionnaires and the lung function measurements between well-controlled and uncontrolled asthma groups

Variable	**Well-controlled asthma group (n=59)**			**Uncontrolled asthma group (n=63)**		
Gender	23 males, 36 females			24 males, 39 females		
Asthma severity	29 mild asthma			4 mild asthma		
	μ*	**sd**	**Min-max**	**μ**	**sd**	**Min-max**
Age (years)	41.20	16.78	19-80	48.06	14.56	18-72
BMI (kg/m^2)	24.95	3.75	18.26-34.29	26.49	4.01	18.71-38.29
NQ	5.47	3.46	0-17	21.43	10.29	1-54
Mini-AQLQ	6.34	0.58	4.27-7.00	4.31	1.27	1.40-6.67
$HADS_{anxiety}$	3.68	3.15	0-13	6.98	4.12	0-18
$HADS_{depression}$	2.20	2.30	0-8	4.90	3.97	0-15
$\%FEV_{1predicted}$	100.90	18.81	61.01-145.02	76.06	24.93	30.20-139.75
FEV1/FEV	81.91	9.44	50.00-95.00	74.49	15.28	31.00-96.00
PEF (L/sec)	5.27	1.42	2.72-9.25	4.06	1.56	1.30-9.74

***μ:** mean value; **sd:** standard deviation; **Min-Max:** minimum and maximum values

6.3.2.2 Comparisons in breathing pattern components between well-controlled and uncontrolled asthma groups

Patients with uncontrolled asthma had higher median values of the examined breathing components (apart from Ti/Te) than the well-controlled group (see Table 6-5). However, only the RR, the $\%COV_{RR}$, the $\%CoV_{Ti/Te}$ and the $\%CoV_{RCampinsp/ABampinsp}$ differed significantly between groups ($p<0.01$, see Table 6-6). The Figure 6-4 shows the boxplots (a, b, c, d, e and f) offering a visual comparison of both the median values and the ranges of measurements of each examined breathing component between the asthma groups.

Table 6-5: Summary of the median, the minimum and the maximum values of the examined breathing components between asthma groups

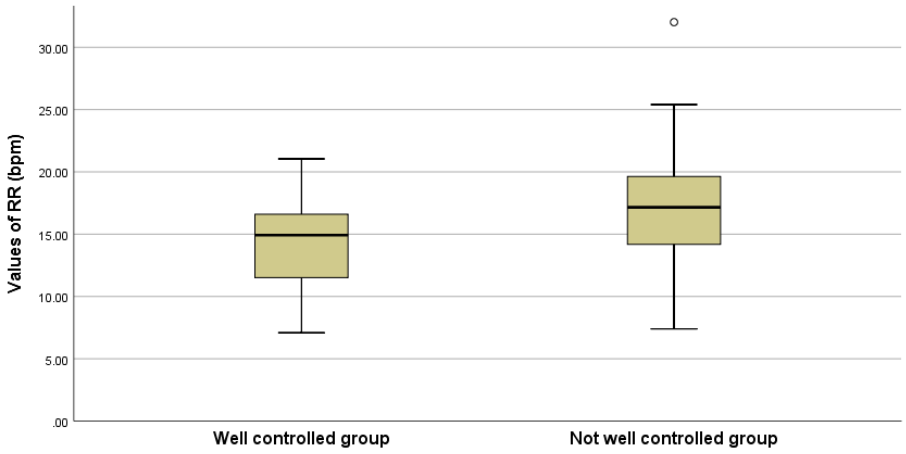
	Well-controlled asthma group (n=59)		Uncontrolled asthma group (n=63)	
Breathing component	**M***	**Min-Max***	**M**	**Min-Max**
RR (bpm)	14.92	7.09-21.05	17.16	7.40-32.02
Ti/Te	0.66	0.40-0.90	0.68	0.40-0.96
$RC_{ampinsp}/AB_{ampinsp}$	1.26	0.46-4.23	1.34	0.36-5.38
$\%CoV_{RR}$	4.79	0.00-23.02	11.73	0.00-29.71
$\%CoV_{Ti/Te}$	19.05	10.49-46.11	33.22	14.28-57.39
$\%CoV_{RCampinsp/ABinsp}$	14.57	7.48-24.58	27.02	8.13-57.78

***M:** median values; **Min-Max:** minimum and maximum values

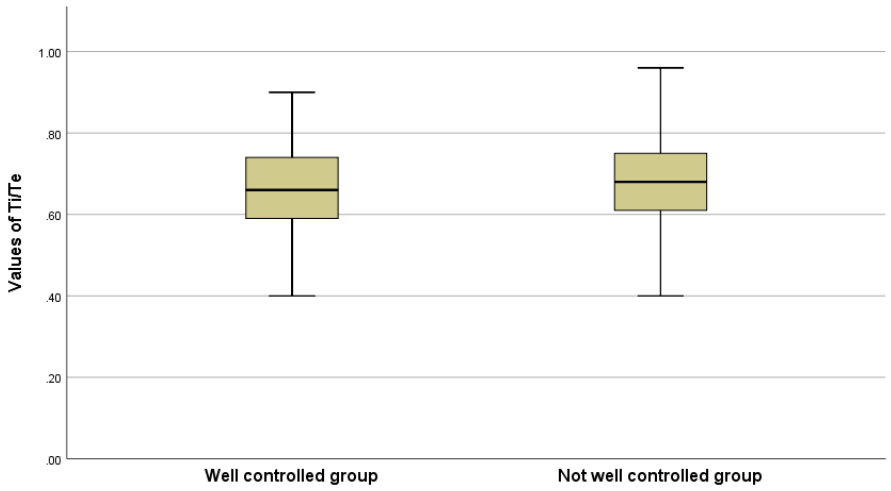
Table 6-6: Summary of the results of the Mann-Whitney U test after making comparisons in breathing pattern components between asthma groups

	Well controlled group(n=59)	Not well controlled group(n=63)		
Breathing component	**Mean Rank**	**Mean Rank**	**Mann-Whitney U**	**Sig**
RR (bpm)	49.92	72.35	1175	0.000*
Ti/Te	58.63	64.19	1689	0.385
$RC_{ampinsp}/AB_{ampinsp}$	60.36	62.57	1791	0.729
$\%CoV_{RR}$	41.10	80.60	655	0.000*
$\%CoV_{Ti/Te}$	40.28	81.37	606	0.000*
$\%CoV_{RCampinsp/ABampinsp}$	43.75	78.13	811	0.000*

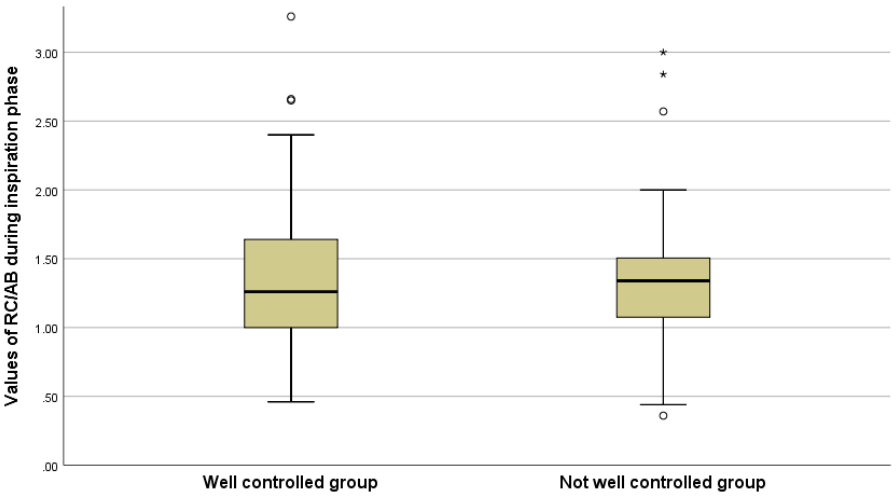
starred (*) values are significant results at $p<0.01$ after using Bonferroni correction for multiple t-tests


Values of RR (bpm)
30.00
25.00
20.00
15.00
10.00
5.00
.00
Well controlled group
Not well controlled group

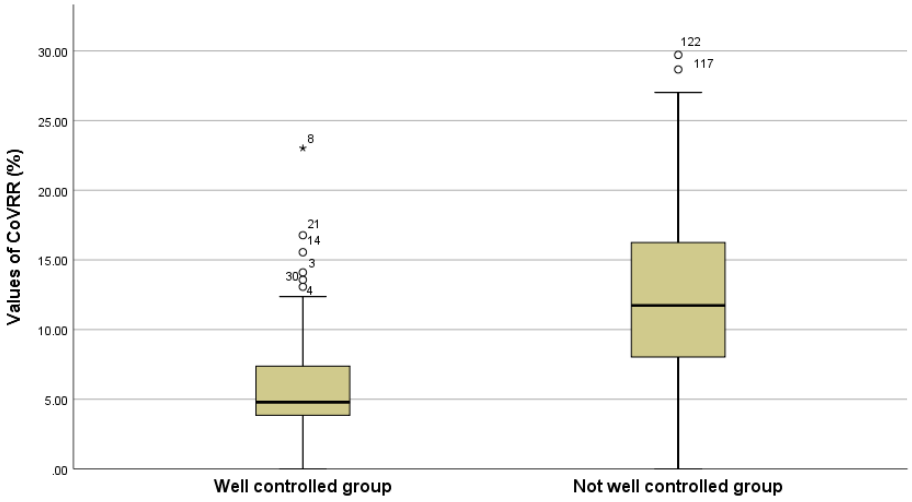
(a)


Values of Ti/Te
1.00
.80
.60
.40
.20
.00
Well controlled group
Not well controlled group

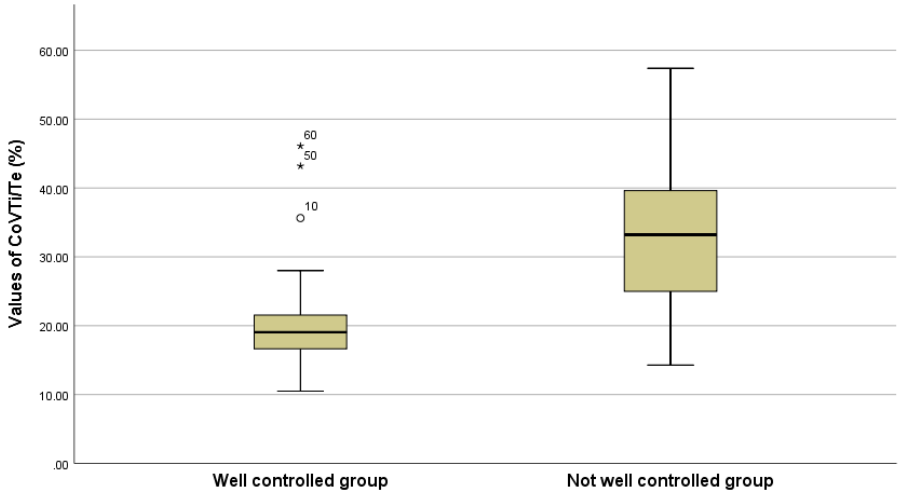
(b)


Values of RC/AB during inspiration phase
3.00
2.50
2.00
1.50
1.00
.50
.00
Well controlled group
Not well controlled group

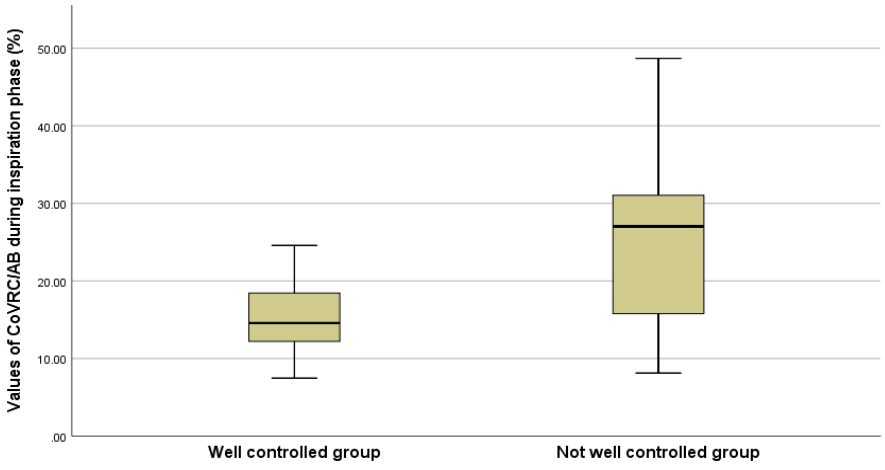
(c)



(d)



(e)



(f)

Figure 6-4: The Boxplots for the examined breathing pattern component between well controlled and uncontrolled asthma groups. (a) RR, (b) Ti/Te, (c) $RC_{ampinsp}/AB_{ampinsp}$, (d) $\%CoV_{RR}$, (e) $\%CoV_{Ti/Te}$ and (f) $\%CoV_{RCampinsp/ABampinsp}$. Circles or stars in the boxplots represent identified outliers within the groups.

6.3.2.3 Predictions of asthma control using the absolute measurements of the examined breathing components

According to the obtained values of tolerance and the Variance Inflation Factor (VIF) (see Table 6-7), there was no violation of assumption of perfect multicollinearity, and a weak significant correlation was found only between the absolute measurements of the RR and the Ti/Te (r 0.245, sig 0.000). Multiple logistic regression results showed that absolute measurements of the RR, the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp}$ could not predict asthma control (see Table 6-8). The use of the specific predictors could significantly affect the model's predictive power compared to the model including only the beta constant (B_0 0.07 Chi-square 11.621 Sig 0.007 $p<0.05$). However, the model did not fit well the data (R^2 0.09) showing poor prediction.

Only the regression coefficient of the RR was found to be significantly greater than zero, making a significant contribution to this regression model (b1 0.16 Wald statistic 9.292 Sig 0.002). However, there was violation of the assumption of linearity between the RR and the log of the outcome variable (Wald statistic 9.623, Sig 0.002, $p<0.05$). No influential cases biasing this regression model were identified (standardised residuals <2 and Cook's distance<1).

Table 6-7: The values of tolerance and the Variance Inflation Factor (VIF) after using collinearity statistics for regression model 1

Regression model 1	Tolerance*	VIF*
RR	0.932	1.073
Ti/Te	0.933	1.071
$RC_{ampinsp}/AB_{ampinsp}$	0.987	1.013

*a tolerance value< 0.1 and a VIF value>10 cause concerns about presence of multicollinearity

Table 6-8: The results of prediction of asthma control using the absolute measurements of the examined breathing pattern components in a sample of 122 asthma patients

		95% CI for Odds Ratio			
Predictors	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig.**
RR (bpm)	0.16(0.05)	1.06	1.17	1.30	0.002*
Ti/Te	0.10 (1.79)	0.03	1.10	37.36	0.954
$RC_{ampinsp}/AB_{ampinsp}$	0.07(0.28)	0.62	1.07	1.87	0.801

B_0= 0.07, R^2: 0.09, R: 0.12, -2LL:157.38. *starred value was found a significant predictor at significance level $p<0.05$

6.3.2.4 Predictions of asthma control using the within-individual variability (%CoV) of the examined breathing components

In contrast to the above findings, the %CoV of all examined breathing components was found to predict asthma control. The Table 6-9 provides the findings of multiple binary logistic regression analysis using the regression model including the %CoV of the examined breathing components. A positive multiple correlation coefficient (R 0.59) was found between the %CoV of all examined breathing components and asthma control. The predictive power of this regression model was significantly better than this including only the beta constant (B_0 0.07 Chi-square 72.12 sig 0.000 $p<0.05$). Good fit of this regression model was found, accounting for 45% of the variance in the ACQ_{7item}. All beta coefficients of this regression model were found to be significantly greater than zero (see Table 6-9), suggesting that the $\%CoV_{RR}$, the $\%CoV_{Ti/Te}$ and the $\%CoV_{RCampinsp/ABampinsp}$ were significant predictors of asthma control. The odds ratios of the three predictors were found >1, showing that high %CoV of the examined breathing pattern components increases the odds of uncontrolled asthma.

There was not perfect multicollinearity among predictors causing no bias to this regression model (see Appendix C). Only 3% of the total cases had absolute values of standardised residuals >2 and Cook's distance >1. However, there were not cases with standardised residuals >2.5, which could be considered as extreme influential cases and there were no more than 5% of the total cases with standardised residuals >2. Furthermore, the assumption of linearity between the log of the outcome and each predictor of this regression model was met (see Appendix C).

Table 6-9: The results of prediction of asthma control using the within-individual variability (%CoV) of the examined breathing pattern components in a sample of 122 patients with asthma

		95% CI for Odds Ratio			
Predictors	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig.**
$\%CoV_{RR}$(bpm)	0.15 (0.05)	1.05	1.16	1.29	0.000*
$\%CoV_{Ti/Te}$	0.10 (0.03)	1.04	1.11	1.18	0.001*
$\%CoV_{RC/ABinsp}$	0.09 (0.04)	1.07	1.10	1.25	0.005*

B_0= 0.07, R^2: 0.45, R: 0.59, -2LL:96.87. *starred values were found significant results at $p<0.05$

6.3.2.5 A post-hoc analysis: The sensitivity, the specificity and the ROC curve of the regression model including the %CoV of the breathing components

The Table 6-10 is a classification table showing how well regression model including the %CoV of the examined breathing components differentiated well-controlled and uncontrolled asthma in a sample of 122 patients. The model correctly classified 53 patients who had well-controlled asthma but misclassified 6 of them. The model also correctly classified 48 patients with uncontrolled asthma, but it misclassified 15 of them. The regression model's sensitivity and specificity were estimated 77.94% and 88.88% respectively. The Youden's index (J) was estimated 0.67, suggesting it as a relatively good classifier.

Table 6-10: The classification table for the regression model including the %CoV of the examined breathing pattern components

	Predicted levels of asthma control using $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCampinsp/ABampinsp}$	
Observed levels of asthma	Well controlled asthma	Uncontrolled asthma
Well controlled asthma (n=59)	53	6
Uncontrolled asthma (n=63)	15	48

The Figure 6-5 shows the ROC curve of this regression model and the Figure 6-6 shows the individual ROC curves for each predictor of this regression model. The Table 6-11 summarises the results regarding the Area Under the Curve (AUC) for the %CoV of each breathing component used to evaluate asthma control. Based on the ROC curve of regression model, the %CoV of the examined breathing components could discriminate patients with well-controlled asthma from those with uncontrolled asthma better than chance level (shown as a red line in Figure 6-4). The corresponding AUC was estimated 0.895 (95%CI [0.84, 0.95], Sig 0.000, $p<0.05$).

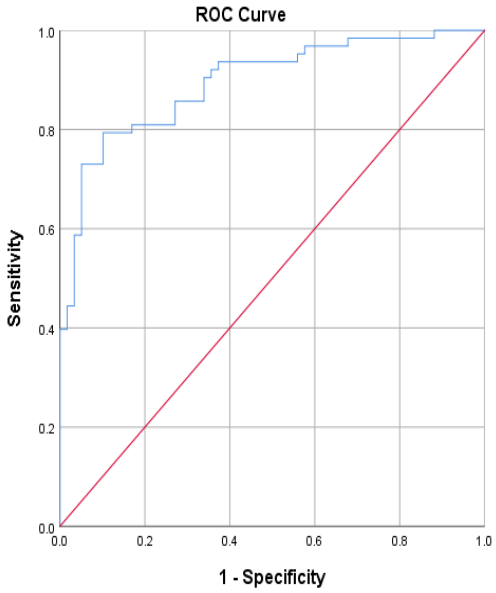


Figure 6-5: The ROC curve of the regression model which included the %CoV of the examined breathing pattern components

Based on the individual ROC curves (see Figure 6-6), the %CoV of each examined breathing pattern component could discriminate between patients with well-controlled and uncontrolled asthma, even though $\%CoV_{RR}$ and $\%CoV_{Ti/Te}$ were found to have better discriminant accuracy than $\%CoV_{RCampinsp/ABampins}$. The Table 6-12 provides several cut-off points (plus values of sensitivity and false positive rates) for the %CoV of each examined breathing component to discriminate between patients with well-controlled and uncontrolled asthma. The values of the examined breathing components, which were nearest to the upper left corner of each ROC curve, were chosen as optimal cut-off points.

A cut-off point >7.40% was found as an optimal cut-off for the $\%CoV_{RR}$ having 84.10% chances to indicate correctly uncontrolled asthma and 76.30% chances to indicate correctly well-controlled asthma. Similarly, a cut-off point >21.66% was estimated as an optimal cut-off point for the $\%CoV_{Ti/Te}$ with sensitivity and specificity being 82.50% and 76.30% respectively. A cut-off point >18.96% was considered as an optimal cut-off point for the $\%CoV_{RCampinsp/ABampinsp}$ with sensitivity and specificity being 71.40% and 78.00% respectively.

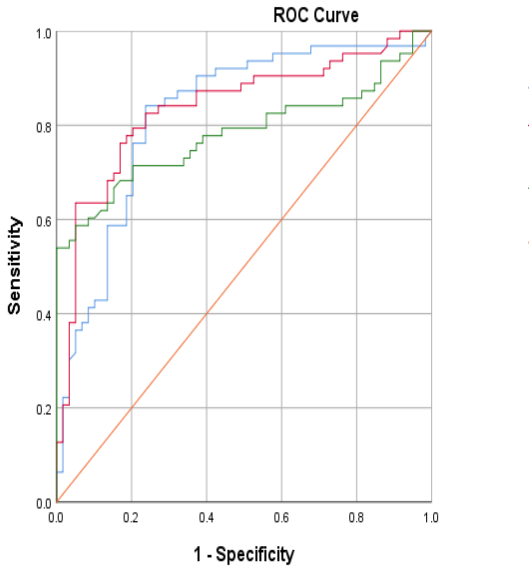


Figure 6-6: The individual ROC curves of the %CoV for each examined breathing component used to discriminate between well-controlled and uncontrolled asthma. The blue line, the red line and the green line are the ROC curves for $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCampinsp/ABampinsp}$ respectively.

Table 6-11: The results of the Area Under the Curve (AUC) for the %CoV of each examined breathing component

Breathing components	**AUC***	**Std Error**	**95%CI Lower-upper**	**Sig.**
$\%CoV_{RR}$	0.824	0.039	0.747-0.900	0.000*
$\%CoV_{Ti/Te}$	0.837	0.038	0.763-0.911	0.000*
$\%CoV_{RCampinsp/ABampinsp}$	0.782	0.044	0.696-0.868	0.000*

***AUC:** Area Under the Curve; starred values were considered significant results at $p<0.05$

Table 6-12 Several cut-off points for the %CoV of each breathing component used to evaluate asthma control in a sample of 122 asthma patients

$\%CoV_{RR}$			$\%CoV_{Ti/Te}$			$\%CoV_{RCampinsp/ABampinsp}$		
Cut-off points	Sensitivity	False positive rate (1-specificity)	Cut-off points	Sensitivity	False positive rate (1-specificity)	Cut-off points	Sensitivity	False positive rate (1-specificity)
>2.86	0.968	0.966	>14.35	0.984	0.898	>10.19	0.921	0.864
>3.85	0.968	0.746	>15.21	0.952	0.814	>11.54	0.857	0.797
>4.78	0.921	0.508	>16.64	0.937	0.746	>13.71	0.825	0.576
>5.79	0.905	0.390	>17.45	0.905	0.678	>14.54	0.794	0.508
>6.69	0.857	0.305	>20.71	0.841	0.322	>16.46	0.714	0.305
>7.40	0.841	0.237	>21.66	0.825	0.237	>18.90	0.714	0.220
>8.10	0.730	0.203	>25.33	0.714	0.169	>20.10	0.635	0.136
>9.15	0.635	0.186	>29.27	0.619	0.051	>21.67	0.587	0.068

The cut-off points, coloured as red, are suggested as the optimal cut-off points for each examined breathing component as based on their individual ROC curves

6.3.2.6 Associations between breathing pattern components and asthma control within subgroups

Bivariate correlation was sought between the examined breathing components and asthma control within subgroups to check consistency of above identified associations between these variables. The subgroups were: 1) female group (n=75), 2) male group (n=47) and 3) moderate-to-severe group (n=89). Significant correlations were found between previously identified significant predictors and asthma control within all subgroups, showing consistency among the results (see Table 6-13).

In the female group and moderate-to-severe asthma group, the %CoV of the examined breathing components was significantly correlated with asthma control ($p<0.05$, see Table 6-13). The RR was also found to be significantly correlated with asthma control in these subgroups. In the male subgroup, significant associations were also found between the %CoV of the examined breathing components and asthma control (see Table 6-13). However, the RR was not significantly associated with asthma control in males unlike other subgroups and this may be due a smaller sized subgroup than the others.

Table 6-13: The results about correlation coefficients between the breathing pattern components and asthma control within the study's subgroups

Breathing components	**Female group (n=75)** r (Sig)	**Male group (n=47)** r (Sig)	**M-S* group (n=89)** r (Sig)
RR (bpm)	0.415 (0.000)*	0.171 (0.125)	0.454 (0.000)*
Ti/Te	0.183 (0.058)	0.060 (0.345)	0.024 (0.421)
$RC_{ampinsp}/AB_{ampinsp}$	-0.072 (0.271)	-0.198 (0.091)	-0.040 (0.368)
%CoVRR	0.496 (0.000)*	0.662 (0.000)*	0.596 (0.000)*
$\%CoV_{Ti/Te}$	0.573 (0.000)*	0.577 (0.000)*	0.544 (0.000)*
$\%CoV_{RCampinsp/ABampinsp}$	0.465 (0.000)*	0.543 (0.000)*	0.420 (0.000)*

***M-S group:** moderate to severe asthma group; Correlation coefficients were obtained using bivariate Spearman correlation; starred values are significant results at $p<0.05$

6.3.3 Results for the presence of dysfunctional breathing

6.3.3.1 Comparisons in the examined breathing components between patients with absence or presence of dysfunctional breathing (DB)

From the total sample, 63 patients were found as having no DB based on a NQ score of <10 and 59 patients were considered as having possible DB based on an NQ score of ≥10. From those with NQ <10, 37 patients were females and 36 patients had moderate to severe asthma. On the other hand, from those with NQ scores ≥10, 38 patients were females and 53 patients had moderate-to-severe asthma. The table 6-14 provides a summary of the median values of breathing pattern components between groups with different NQ scores. There were significant differences in the RR and the %CoV of each examined breathing component between patients with NQ <10 and those with NQ ≥10 (see Table 6-15). Patients with NQ ≥10 had increased both the RR and the %CoV of each examined breathing component.

Table 6-14: The median values of the examined breathing pattern components between patients with absence of dysfunctional breathing and those with possible presence of dysfunctional breathing

	Patients with NQ<10 (n=63) NO DB		**Patients with NQ≥10 (n=59) Possible DB**	
Breathing component	**M***	**Min-Max**	**M***	**Min-max**
RR (bpm)	14.92	7.09-21.05	17.40	7.40-32.02
Ti/Te	0.65	0.40-0.90	0.68	0.44-0.96
$RC_{ampinsp}/AB_{ampinsp}$	1.31	0.46-4.23	1.32	0.36-5.38
$\%CoV_{RR}$	5.73	0.00-23.87	11.06	0.00-29.71
$\%CoV_{Ti/Te}$	19.54	10.49-56.16	31.25	14.28-57.39
$\%CoV_{RCampinsp/ABampinsp}$	14.75	7.48-47.26	21.74	8.13-57.78

*M: median values

Table 6-15: The results of the Mann-Whitney U test used to compare the examined breathing pattern components between patients with absence of dysfunctional breathing and those with possible presence of dysfunctional breathing

	Patients with NQ <10 (n=63) NO DB	**Patients with NQ ≥10 (n=59) Possible DB**		
Breathing components	**Mean Rank**	**Mean Rank**	**Mann-Whitney U**	**Sig.**
RR (bpm)	50.18	73.58	1145.500	0.000*
Ti/Te	56.25	67.10	1528.000	0.090
$RC_{ampinsp}/AB_{ampinsp}$	63.06	59.83	1760.000	0.614
$\%CoV_{RR}$	47.81	76.12	996.000	0.000*
$\%CoV_{Ti/Te}$	46.83	77.16	934.5000	0.000*
$\%CoV_{RCampinsp/ABampinsp}$	48.86	75.00	1062.000	0.000*

Starred (*) values were found significant results at p<0.01 after Bonferroni correction for multi t-tests

6.3.3.2 Predictions of the presence of dysfunctional breathing using the examined breathing pattern components

The results regarding predictions of the presence of DB were consistent to those found for the primary outcome variable of this correlational study (asthma control). Use of the absolute measurements of the RR, Ti/Te and RCampinsp/ABampinsp were found not to predict presence of DB (see Table 6-16). Although absolute measurements of the breathing pattern components could improve the predictive power of the regression model compared to this including only the beta constant (B0 -0.07 Chi-square 13.210 sig 0.004, p<0.05), this regression model did not fit well the data (R2 0.10, -2LL155.79). However, the RR made a significant contribution to this model with its beta coefficient being significantly greater than zero (see Table 6-16). Despite the absence of influential cases for this regression model, the assumption of linearity between the RR and the log of the outcome variable was violated (Wald statistic p <0.05, see Appendix C).

Table 6-16: The results of prediction of the presence of dysfunctional breathing using the absolute measurements of the examined breathing pattern components in a sample of 122 asthma patients

		95% CI for Odds Ratio			
Predictors	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig**
RR (bpm)	0.15 (0.05)	1.05	1.16	1.28	0.004*
Ti/Te	1.92 (1.83)	0.19	6.84	48.20	0.294
$RC_{ampinsp}/AB_{ampinsp}$	-0.06 (0.28)	0.55	0.94	1.61	0.817

B_0 -0.07, R^2: 0.10, R: 0.14, -2LL:155.79; starred (*) value was found a significant result at p<0.05

On the other hand, the %CoV of the examined breathing components was found to predict presence of DB (see Table 6-17). All beta coefficients of this regression model were found significantly greater than zero (see Table 6-17). Based on odds ratios, increased %CoV of the examined breathing pattern components was likely to increase the probability of DB being present. The assumption of linearity between all predictors of this regression model and the log of the outcome variable was not violated (Wald statistic p >0.05, see Appendix C).

Table 6-17: The results of prediction of presence of dysfunctional breathing using the %CoV of the examined breathing pattern components in a sample of 122 patients with asthma

		95% CI for Odds Ratio			
Predictors	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig**
$\%CoV_{RR}$	0.08 (0.04)	1.02	1.08	1.16	0.012*
$\%CoV_{Ti/Te}$	0.04 (0.02)	1.01	1.04	1.09	0.022*
$\%CoV_{RCampinsp/ABampinsp}$	0.05 (0.03)	1.00	1.05	1.11	0.023*

B_0 -0.07, R^2: 0.25, R: 0.29, -2LL:139.47. Starred (*) values were found to be significant at p<0.05

6.3.3.3 A post-hoc analysis: The sensitivity, specificity and ROC curve for the %CoV of the examined breathing pattern components

The Table 6-18 provides a classification table showing how well the regression model including the %CoV of the examined breathing pattern components, could detect presence of DB in a sample of 122 asthma patients. The model identified correctly 52 patients with absence of DB but misclassified 11 of them. It also correctly classified 40 asthma patients with the presence of DB, but misclassified 19 of them. The sensitivity and specificity of the regression model were estimated to be 73.24% and 78.43% respectively. The Youden's index (J) was estimated 0.52. The Figure 6-7 provides the ROC curve of this regression model. The AUC was estimated 0.79 (95%CI [0.71, 0.87], sig 0.000, p<0.05) supporting the use of the %CoV of examined breathing pattern components as a classifier for the presence of DB in patients with asthma.

Table 6-18: The classification table for detecting presence of dysfunctional breathing using the %CoV of the breathing pattern components in a sample of 122 asthma patients

	Predicted presence of DB using $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCanpisnp/ABampinsp}$	
Observed presence of DB	Absence of DB	Presence of DB
Absence of DB (n=63)	52	11
Presence of DB (n=63)	19	40

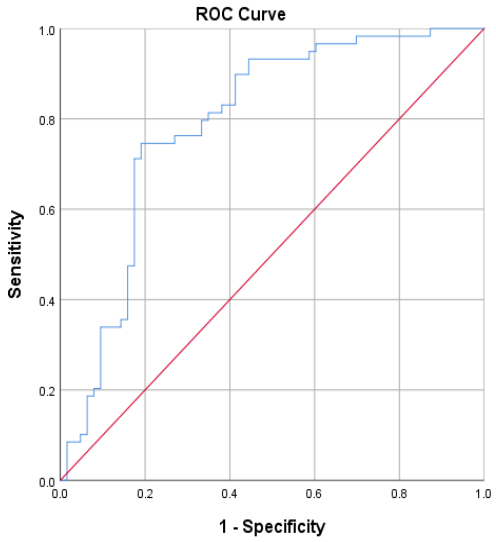


Figure 6-7: The ROC curve of the regression model including the %CoV of the examined breathing components used to evaluate presence of dysfunctional breathing

The Figure 6-8 provides the individual ROC curves of the %CoV for each examined breathing component used to evaluate presence of DB. Although all breathing components could discriminate asthma patients with DB from those with absence of DB better than chance level (see Table 6-19), $\%CoV_{RCampinsp/ABampinsp}$ was not found to be an accurate and sensitive parameter compared to others (see Figure 6-8). Optimal individual cut-off point of $\%CoV_{RCampinsp/ABampinsp}$ was >27.46% with sensitivity and specificity being 57.60% and 60.30% respectively.

Table 6-19: The results of the Area Under the Curve (AUC) for the %CoV of each examined breathing component in a sample of 122 asthmatic patients

Breathing components	AUC	Std Error	95%CI Lower-upper	Sig.
$\%CoV_{RR}$	0.732	0.046	0.642-0.822	0.000*
$\%CoV_{Ti/Te}$	0.749	0.046	0.658-0.840	0.000*
$\%CoV_{RCampinsp/ABampinsp}$	0.618	0.051	0.519-0.718	0.025*

*starred values were considered significant at p<0.05

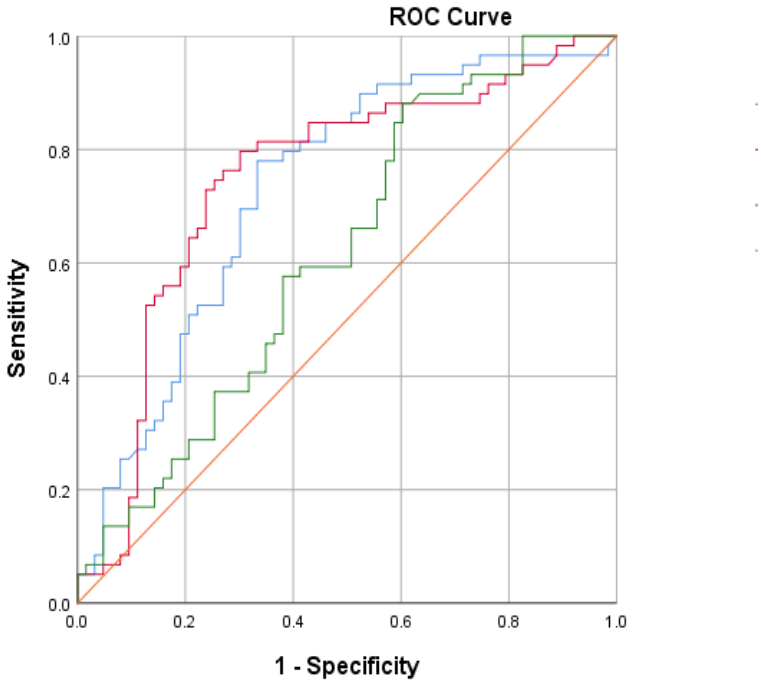


Figure 6-8: The individual ROC curves for the %CoV of each breathing component used to monitor presence of dysfunctional breathing in a sample of 122 asthma patients. The blue, the red and the green lines are the ROC curves for $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCampinsp/ABampinsp}$ respectively.

Table 6-20: Overview of several cut-off points for the CoV% of each examined breathing component used to monitor dysfunctional breathing

$\%CoV_{RR}$			$\%CoV_{Ti/Te}$			$\%CoV_{RCampins/ABampinsp}$		
Cut-off points	Sensitivity	False positive rate (1-specificity)	Cut-off points	Sensitivity	False positive rate (1-specificity)	Cut-off points	Sensitivity	False positive rate (1-specificity)
>3.85	0.966	0.762	>14.55	0.966	0.889	>16.76	0.932	0.730
>4.31	0.932	0.698	>15.71	0.932	0.825	>21.21	0.797	0.587
>4.78	0.898	0.556	>17.76	0.881	0.698	>25.33	0.610	0.508
>5.67	0.847	0.508	>19.64	0.847	0.492	>26.59	0.593	0.460
>7.40	0.780	0.333	>21.66	0.797	0.302	>27.46	0.576	0.397
>8.39	0.610	0.286	>24.39	0.729	0.238	>30.25	0.441	0.349
>10.45	0.525	0.238	>26.75	0.576	0.190	>31.59	0.390	0.317

Cut-off points coloured as red are suggested as optimal cut-off points for each examined breathing component to monitor presence of DB as based on individual ROC curves

The accuracy of the $\%CoV_{RCampinsp/ABampinsp}$ to evaluate presence of DB was improved, when NQ scores between 10 and 17 were excluded. These cases were considered as influential cases (n=21) based on their standardised residuals. In a reduced sample of 101 asthma patients, the AUC corresponding to the $\%CoV_{RCampinsp/ABampinsp}$ was re-estimated at 0.748 (95%CI 0.642-0.854, Sig 0.000, p<0.05). Similar AUC were found for both $\%CoV_{RR}$ and $\%CoV_{Ti/Te}$ (see Figure 6-9, Table 6-21). The optimal cut-off point for $\%CoV_{RC/ABinsp}$ was re-estimated at >15.86% with improved sensitivity (76.30%) and specificity (61.90%). Also optimal cut-off points for the $\%CoV_{RR}$ and the $\%CoV_{Ti/Te}$ were estimated >7.40% (86.80% sensitivity, 66.70% specificity) and >22.01% (73.70% sensitivity, 69.80% specificity) respectively.

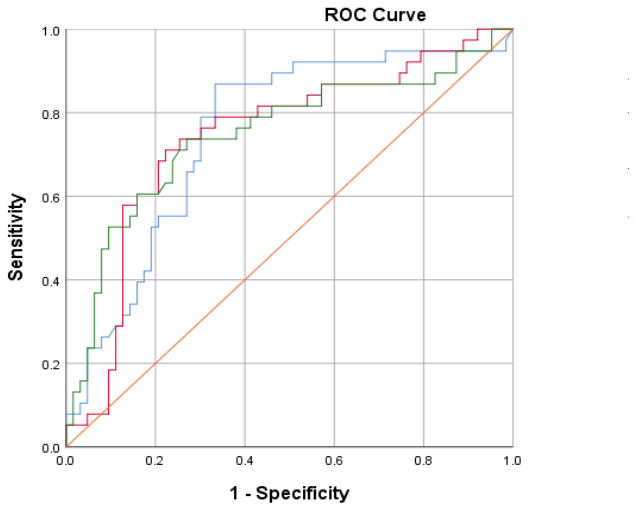


Figure 6-9: The individual ROC curves of the %CoV for each breathing pattern component used to monitor DB in a sample of 101 asthma patients. The blue, red and green lines are the individual ROC curves for the $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCampinsp/ABampinsp}$ respectively.

Table 6-21: The results of Area Under the Curve for $\%CoV_{RR}$ and $\%CoV_{Ti/Te}$ used to monitor dysfunctional breathing in a sample of 101 asthmatic patients

Breathing components	AUC	Std Error	95%CI Lower-upper	Sig.
$\%CoV_{RR}$	0.752	0.051	0.653-0.852	0.000*
$\%CoV_{Ti/Te}$	0.742	0.053	0.638-0.846	0.000*
$\%CoV_{RC/ABinsp}$	0.748	0.050	0.642-0.854	0.000*

*starred values were considered significant at p<0.05

6.3.4 Predictions of lung function measurements using the examined breathing pattern components

The following sections provide the results regarding predictions of lung function measurements via the use of regression model 1 (absolute measurements of breathing components) and 2 (%CoV of the breathing components). The results about meeting assumptions (such as linearity, homoscedasticity, independent errors and normality of residuals) after applying each model are provided in the Appendix C.

6.3.4.1 Prediction of $\%FEV_{1predicted}$ via the use of breathing pattern components

The Table 6-22 and Table 6-23 provide the results regarding predictions of the $\%FEV_{1predicted}$ using regression model 1 and 2. Neither absolute measurements nor %CoV of the examined breathing components could predict the $\%FEV_{1predicted}$. The use of RR, Ti/Te and $RC_{ampinsp}/AB_{ampinsp}$ accounted only for 10% of the variation in the $\%FEV_{1predicted}$, showing bad fit of the model. Similarly, the $\%CoV_{RR}$, the $\%CoV_{Ti/Te}$ and the $\%CoV_{RCampinsp/ABampinsp}$ accounted for 1% more in the variance in this outcome showing also poor prediction (R^2: 0.11). The adjusted R^2 of the regression models 1 and 2 were estimated 0.07 and 0.09 respectively. They were slightly smaller than the R^2 of the regression models. The shrinkage of adjusted R^2 showed that regression models 1 and 2 would account for approximately 2.3% and 2.2% less in the variance of the $\%FEV_{1predicted,}$ if they were derived from a general population rather than the sample of the study.

Despite poor predictions of the $\%FEV_{1predicted}$, small but still significant F-ratios were found for both regression models (model 1: F 4.275 Sig 0.007; model 2: F4.975 Sig 0.003, $p<0.05$). This indicated an improvement in prediction of the $\%FEV_{1predicted}$ after fitting each model. Improvement in models' predictive power was based on the presence of significant predictors in each model. For regression model 1, negative unstandardized beta coefficient of the RR was found significantly greater than zero (model's b1 -1.55 $p<0.05$) supporting a negative relationship between the RR and the $\%FEV_{1predicted}$. For regression model 2, only the $\%CoV_{Ti/Te}$ was found a significant predictor of the $\%FEV_{1predicted}$ (unstandardized b1 -0.565 sig 0.015 $p<0.05$).

Only 3% and 4% of the total cases were considered as influential cases for regression model 1 and 2 respectively. Similar number of influential cases were identified for each regression model used to predict the FEV_1/FVC and the PEF. This was less than 5% of the total cases causing no concern about any bias in the regression models. However, large 95%CI and standard errors of B were identified for the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp}$ when used to predict not only the $\%FEV_{1predicted}$ (see Table 6-22), but also the FEV_1/FVC and the PEF (see sections 6.3.4.2 and 6.3.4.3). This raised concerns about untrustworthy regression coefficients for the specific predictors.

Table 6-22: The results of prediction of the $\%FEV_{1predicted}$ using the absolute measurements of breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-1.55 (0.54)	-0.259	-2.63	-0.48	0.005*
Ti/Te	3.13 (20.57)	0.146	-7.60	43.86	0.110
$RC_{ampinsp}/AB_{ampinsp}$	5.21 (3.24)	0.142	-1.20	11.62	0.110

B_0 82.29, R^2 0.10, R 0.31, Adjusted R^2 0.07, F-ratio 4.275 (Sig0.007); starred value is a significant result at $p<0.05$

Table 6-23: The results of prediction of the $\%FEV_{1predicted}$ using the %CoV of breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-0.47 (0.39)	-0.11	-1.25	-0.31	0.231
$\%CoV_{Ti/Te}$	-0.56 (0.23)	-0.25	-1.02	-0.11	0.015*
$\%CoV_{RCampinsp/ABampinsp}$	-0.08 (0.25)	-0.03	-0.58	0.41	0.744

B_0 82.29, R^2 0.11. R 0.33, adjusted R^2 0.09, F-ratio 4.975 (Sig 0.003), starred value is a significant result at $p<0.05$

6.3.4.2 Prediction of the FEV_1/FVC via the use of the examined breathing pattern components

None of the examined breathing pattern components could predict the FEV_1/FVC as determined by small R^2 and no significant beta coefficients of predictors in each regression model (see Table 6-24 and Table 6-25). No improvement in predictive power of any of the applied regression models was found with their F-ratios not being significant ($p>0.05$).

Table 6-24: The results for prediction of the FEV_1/FVC using the absolute measurements of breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-0.39 (0.293)	-0.12	-0.97	0.19	0.189
Ti/Te	2.37 (11.11)	0.02	-19.62	14.37	0.831
$RC_{ampinsp}/AB_{ampinsp}$	2.90 (1.75)	0.15	-0.56	6.37	0.099

B_0 78.10 , R^2 0.09, R 0.201, adjusted R^2 0.02, F-ratio 1.655 (Sig 0.181); significance at $p<0.05$

Table 6-25: The results for prediction of the FEV_1/FVC using the %CoV of the breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-0.23 (0.21)	-0.11	-0.66	-0.19	0.277
$\%CoV_{Ti/Te}$	-0.13 (0.12)	-0.12	-0.38	0.11	0.284
$\%CoV_{RCampinsp/ABampinsp}$	-0.04 (0.12)	-0.01	-0.28	0.26	0.954

B_0 83.99, R^2 0.04. R 0.19, adjusted R^2 0.01, F-ratio 1.470 (Sig 0.226); significance at $p<0.05$

6.3.4.3 Prediction of the PEF using the examined breathing pattern components

Neither absolute measurements nor %CoV of the breathing components were found to predict the PEF (see Table 6-26 and Table 6-27). Improvement in predictive power of the models was found after using only the %CoV of breathing components (regression model 2: F 4.736 Sig 0.004, $p<0.05$) with the $\%CoV_{Ti/Te}$ being the only significant predictor for the PEF. A small but still significant negative correlation (r -0.177 sig 0.026, $p<0.05$) was also found between the RR and the PEF.

Table 6-26: The results of prediction of the PEF using the absolute measurements of breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-7.64 (3.54)	-0.20	-14.67	-0.62	0.033*
Ti/Te	7.96 (134.42)	0.10	-28.22	40.16	0.307
$RC_{ampinsp}/AB_{ampinsp}$	-3.16 (21.16)	-0.01	-45.06	38.75	0.882

B_0 494.16, R^2 0.04, R 0.20, adjusted R^2 0.02, F-ratio 1.635 (Sig 0.185); starred value is significant result at $p<0.05$

Table 6-27: The results of prediction of the PEF using the %CoV of the breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-2.15 (2.50)	-0.08	-7.11	-0.81	0.392
%CoVTi/Te	-4.02 (1.45)	-0.29	-6.89	-1.16	0.006*
$\%CoV_{RCampsinp/ABampinsp}$	-0.03 (1.59)	0.01	-3.17	3.12	0.989

B_0 594.15, R^2 0.11, R 0.33, adjusted R^2 0.09, F-ratio 4.736 (Sig 0.004) starred value is significant result at $p<0.05$

6.3.5 Results for prediction of asthma-related quality of life

The within-individual variability of breathing pattern components was associated with patients' quality of life. Increased $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCampinsp/ABampinsp}$ were found to significantly predict lower mini-AQLQ scores accounting for 26.3% in the variation of mini-AQLQ (see Table 6-29). In contrast, use of the absolute measurements of the examined breathing components was not found to predict poor quality of life accounting only for 6.2% in the variation of the mini-AQLQ (see Table 6-28). Nevertheless, negative unstandardised and standardised coefficients of the RR were found to be significantly greater than zero, indicating it as a significant predictor of this outcome variable (see Table 6-28).

Table 6-28: The results of prediction of asthma-related quality of life using the absolute measurements of breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-0.07 (0.03)	-0.21	-0.13	-0.01	0.022*
Ti/Te	-0.81 (1.18)	-0.06	-3.15	1.52	0.491
$RC_{ampinsp}/AB_{ampinsp}$	-0.18 (0.19)	-0.09	-0.54	0.19	0.344

B_0 7.20, R^2 0.06, R 0.25, adjusted R^2 0.04, F-ratio 2.587 (Sig 0.049) starred value is a significant result at $p<0.05$

Table 6-29: The results of prediction of asthma-related quality of life using the %CoV of breathing pattern components

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Predictors	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-0.08 (0.02)	-0.34	-0.12	-0.04	0.000*
$\%CoV_{Ti/Te}$	-0.03 (0.01)	-0.22	-0.05	-0.02	0.020*
$\%CoV_{RCampinsp/ABampinsp}$	-0.02 (0.01)	-0.08	-0.04	-0.01	0.034*

B_0 7.02, R^2 0.26, R 0.51, adjusted R^2 0.25, F-ratio 14.056 (Sig 0.000). Starred values are significant results at $p<0.05$

6.3.6 Summary of the findings of the correlational study

The correlational study presented in this chapter aimed to identify associations between specific quantifiable breathing pattern components and asthma control. A secondary aim was to examine the use of the quantifiable breathing pattern components as a surrogate marker for other asthma-related outcomes, such as the presence of DB, the lung function measurements and the asthma-related quality of life.

The findings suggest that the %CoV of the examined breathing pattern components (RR, Ti/Te and RC_{amp}/AB_{amp} during both respiratory phases) can predict asthma control and be used as a good classifier for differentiating between well-controlled and uncontrolled asthma. On the other hand,

the absolute measurements of the above breathing pattern components were not found to predict uncontrolled asthma, even though the RR was found to be a significant predictor for this outcome variable.

The above findings are consistent with those found for the presence of DB and asthma-related quality of life. The %CoV of the breathing pattern components (RR, Ti/Te and RC_{amp}/AB_{amp} during both respiratory phases) were found to predict presence of DB in patients with asthma and poor quality of life with their absolute measurements not being found to predict these variables. Furthermore, neither absolute measurements nor %CoV of the examined breathing pattern components were found to predict lung function ($\%FEV_{1predicted}$, FEV_1/FVC and PEF).

6.4 The discussion of the correlational study

6.4.1 The results found for asthma control in relation to current evidence

In the correlational study, patients with uncontrolled asthma showed lower mini-AQLQ scores, higher NQ scores and reduced lung function measurements compared to those with well-controlled asthma. These results are consistent to those clearly found in previous literature regarding associations between uncontrolled asthma and patients quality of life (Chen et al. 2007;Dean et al. 2009; Correia de Sousa et al. 2013), the presence of DB (Agache et al. 2012; Courtney 2017) and declined lung function measurements (Papakosta et al. 2011; Matsunaga et al. 2014). However, this correlational study expands our knowledge about the use of quantifiable breathing pattern components in relation to asthma control.

The findings of this study showed that there were significant differences in the RR, but not in the Ti/Te and the RC_{amp}/AB_{amp} (during either respiratory phases) between well-controlled and uncontrolled asthma groups. In contrast, Tobin et al. (1983b) found no statistically significant differences in the RR among healthy people, symptomatic patients with asthma, and asymptomatic patients. The authors reported that symptomatic asthma patients' average RR were 16.6 bpm. The RR reported by Tobin et al (1893b) in the symptomatic patient group was similar to the RR found in the uncontrolled asthma group of this correlational study (RR: 17.2 bpm), despite the differences in monitoring tools and posture used for breathing pattern recordings between the two studies. A lack of significant results in the study by Tobin et al. (1983b) may be attributed to the small unequal groups. However, significant increased RR (18.7 bpm) in patients with acute symptoms of asthma recorded at the sitting position during resting breathing has been reported by Lennox et al. (1985). This was consistent to the findings of this correlational study. However, none of these authors used a standardised tool for quantifying

levels of asthma control to be predicted by quantifiable breathing pattern components as this correlational study did.

In the correlational study, only absolute measurements of RR were found as a significant predictor of asthma control as measured via the ACQ_{7item}. However, a linear relationship between these variables was not found. This may be related to the presence of patients (n=12) in the well-controlled asthma group having raised RR ≥17 bpm. On the other hand, there were patients (n= 19) within uncontrolled asthma group who had a normal RR (12-15 bpm) or lower. From those with well-controlled asthma but still raised RR, 4 patients had BMI >30kg/m^2 whereas 7 patients scored $HADS_{anxiety}$>8. Previous research has indicated that factors, such as emotional arousal and obesity, can have an impact on breathing pattern components such as the RR (Homma and Masaoka 2008; Chlif et al. 2009). Consequently, these factors could be therefore deemed to be some confounders, which biased the identified non-linear relationship between the RR and the asthma control.

The reasons for observing low or normal RR in patients with uncontrolled asthma (n=19) are not clear. It is possible that this could be due to the SABA use on the day of breathing pattern recordings as self-reported by some patients (n=16). All the patients (n=19) who had uncontrolled asthma and normal or low RR had moderate-to-severe asthma, and 16 of them reported use of SABA on the day of breathing pattern recordings. Due to their asthma severity and their uncontrolled asthma, SABA was used to alleviate their acute asthma symptoms. This could have an impact on breathing patterns and affect the absolute measurements of the RR. Nevertheless, to date, it is not known any associations of the effects of the SABA use (or any other asthma medication) on a range of quantifiable breathing pattern components, including either absolute measurements or the regularity of them over time.

No other absolute measurements of the examined breathing pattern components were found to be significant predictors of asthma control or of any other examined variable of this correlational study. A priori, a shift toward greater RC displacement than AB displacement was expected in patients with uncontrolled asthma. Some previous observational cross-sectional studies examining breathing mechanics in asthma have shown that greater RC displacement and asynchrony between the RC and the AB were moderately correlated with uncontrolled asthma (Courtney et al. 2011; Upton et al. 2012). This inconsistency in findings may be related to the different research protocols used to quantify the THA movements and define asthma control between the present study and the published studies in the literature.

Courtney et al. (2011) used the MARM to measure perceived displacement of upper thorax over lower thorax in individuals with unexplained dyspnoea speculating presence of uncontrolled

asthma. On the other hand, this correlational study used the SLP to provide objective measurements of the proportionality of amplitudes of the compartmental displacements of the THA. Furthermore, Upton et al. (2012) used the RIP to look at the association between the THA asynchrony and asthma control in comparison to this correlational study measuring the proportionality of direct amplitudes of displacements of the RC and the AB areas.

In addition, these contradictory findings could be due to the posture used for monitoring the THA movements in this correlational study. Romei et al. (2010) have indicated that different postures can cause alterations in the THA movements during resting breathing. Increased AB displacement is more likely to be present in the supine posture rather than in the sitting position (Romei et al. 2010). While seated, the abdominal content stretches the abdominal wall, thereby limiting the spontaneous displacement of the diaphragm, and resulting in a mechanical disadvantage of the AB area (Kaneko and Horie 2012). Based on that, a sitting position could therefore be considered as another confounding factor, which could have limited the expected greater AB displacement in patients with well-controlled asthma. Hence, it may have been preferable to assess the absolute measurements of the parameter associated with the THA movements in other postures, such as semi-supine position. This could have avoided any posture effect on breathing mechanics even though the sitting position is one of the routine position for breathing pattern assessments in clinical practice.

In contrast to the above contradictory findings, the breathing pattern variability was found to be a better physiological marker to predict asthma control. The within-individual variability of the RR, the Ti/Te and the RC_{amp}/AB_{amp} (during both respiratory phases) significantly differed between well-controlled and uncontrolled asthma groups. The association identified between these variables was that increased within-individual variability of the examined breathing pattern components could predict uncontrolled asthma. This was a major finding because only a limited body of previously published work has studied breathing pattern variability in relation to asthma control.

Raoufy et al. (2016) examined the within-individual variability of different breathing pattern components compared to those examined in the correlational study of this research. The within-individual variability of the Vt and the breath intervals were assessed by the RIP in the supine position, during 60 minutes, among 40 individuals. The individuals were 10 healthy adults, 10 patients with controlled atopic asthma, 10 patients with uncontrolled atopic asthma and 10 patients with uncontrolled non-atopic asthma. There were several methodological differences between the correlational study and that by Raoufy et al. (2016). These included the quantification of asthma control (use of National Asthma Education and Prevention Program

guidelines to classify participants versus the ACQ_{7item} used in the correlation study) and the posture used to examine breathing pattern components using another form of non-invasive recording technology. Nevertheless, some similar findings were reported without any of these methodological differences causing contradictory findings.

Raoufy et al. (2016) suggested that increased within-individual variability of both Vt and breaths intervals are associated with uncontrolled asthma. This correlational study comes to add knowledge to this research field by suggesting that increased $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCamp/ABamp}$ (during both respiratory phases) can be considered to be some other physiological predictors of uncontrolled asthma, demonstrating a linear relationship with this outcome variable. Different postures and time for breathing pattern recordings were used between the correlational study and that by Raoufy et al. (2016), with 5-minute of recording being sufficient for identifying medium linear association between breathing pattern variability and asthma control.

A 5-minute recording of breathing pattern components was selected in this study, due to the fixed-recording time of the SLP. As mentioned previously, the sitting posture used in this correlational study could have a potential impact on the absolute measurements of some of the examined breathing components, such as the THA movements, but this was not a reason for biasing findings regarding the association between their within-individual variability and asthma control. To date, it is not known whether there is any postural effect on breathing pattern variability compared to this known for the absolute measurements of the THA movements (see section 3.3.2).

Direct comparisons of the strength of multiple correlation coefficient (R 0.59) between the within-individual variability of the examined breathing components and the asthma control could not be made with previous research. However, the correlational study's results are comparable to earlier findings regarding the strength of associations between other physiological markers (lung function measurements and FeNO) and asthma control as measured by ACQ_{7item} (Papakosta et al. 2011; Grzelewska-Rzymowska et al. 2015). Moreover, small but still significant correlations were found between the within-individual variability of the examined breathing components and asthma control in all studied subgroups. This suggests that the identified relationship between these variables may be maintained, irrespective of patients' gender or asthma severity. Raoufy et al. (2016) had previously suggested that the within-individual variability of Vt and breaths intervals can predict asthma control irrespective of asthma phenotype. However, the identified weak correlations between these variables in the correlational study's subgroups could be due to the small number of participants in them. This is the same for the subgroups of this correlational study. Larger sample sizes for these subgroups would be required to perform predictions, rather

than simple correlation analysis, to cross-validate regression results within the examined subgroups.

On the other hand, this correlational study contributes to our current knowledge by supporting that the parallel use of $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCamp/ABamp}$ can be used as a new supplemental physiological classifier for asthma control. This is consistent with previous findings reported by Raoufy et al. (2016), who were the first to indicate that the use of the within-individual variability of Vt and breath intervals could discriminate between patients with well controlled asthma and those with uncontrolled asthma. However, to the best of the researcher's knowledge, this correlational study presented in this thesis can be considered to be the first attempt to provide some individual cut-off points for the variability of the examined breathing pattern components, thereby lacking direct comparisons with previous published evidence.

6.4.1.1 The increased within-individual variability of the examined breathing components in uncontrolled asthma

Identifying causality between the increased within-individual variability of the examined breathing pattern components and the uncontrolled asthma was not possible using an observational cross-sectional study design. The primary aim of this correlational study was to examine whether there was an association between timing parameters, the THA movement and asthma control to understand the usefulness of these breathing components as a physiological marker in asthma management. Since these variables were measured at the same point in time, it may not be possible to distinguish whether increased with-individual variability preceded or followed uncontrolled asthma. Nevertheless, the identified association between these variables may be theorised to be explained by several factors as previously reported by the literature and in line with some observations in this correlational study.

From a physiological perspective, healthy breathing generally consists of a structured variability and some random variability to ensure stability of the respiratory system (Vlemincx et al. 2010). The respiratory system is likely to compare one breath to its predecessor, adjusting the following breath with respect to frequency and volume, and so generate a pattern of breathing (Benchetrit 2000). Despite some degree of random within-individual variability in each component of breathing patterns, the breath-by-breath variations have been found to be consistent within individuals over time, representing the output of a relative stable control of breathing (Shea et al. 1987; Yang 1992). Any alteration in the dynamics of this process can alter the regularity in the components of breathing patterns over time and can indicate potential changes in the respiratory system (Frey et al. 2011; Raoufy et al. 2017). Thus, the increased within-individual variability of

the RR, Ti/Te and RC_{amp}/AB_{amp} (during both respiratory phases) within patients with uncontrolled asthma may reflect alterations in the control of breathing.

Fiamma et al. (2007) examined the breath-by-breath variability of the Vt, the Ti and the Te in only 8 healthy adults, after inducing different levels of CO_2. The authors' reported that hypocapnia caused by the hyperventilation, led to increased variability of the Vt and the timing components. The authors concluded that changes in CO_2 can stimulate chemoreflexes to produce ventilatory re-adjustments, as reflected by the increase in the variability of the examined breathing pattern components. In asthma literature, associations between uncontrolled asthma and hyperventilation (as determined by reduced CO_2, or raised RR or a NQ score ≥23) have been well documented (Barker and Everard 2015; Agache et al. 2012, Courtney 2017). The results of the correlational study are consistent with these findings. The uncontrolled asthma group had higher mean NQ score and significantly increased RR, compared to well-controlled asthma group, suggesting possible presence of hyperventilation within the uncontrolled asthma group.

Patients with uncontrolled asthma are likely to hyperventilate in response to increased metabolic requirements caused by the several mechanisms underlying asthma during symptomatic periods (Courtney 2017). During such periods, ventilatory re-adjustments are made to try to restore CO_2 to its equilibrium level (Schiff 1980). This may be partially reflected by the increased within-individual variability of the examined breathing pattern components of this correlational study. However, direct measurements of CO_2 were not obtained during this study, so the presence of hyperventilation could only be assumed from the raised NQ scores and the RR observed in the uncontrolled asthma group.

The increased within-individual variability of the examined breathing pattern components in patients with uncontrolled asthma may be a response of the central respiratory centre to increased metabolic requirements. This in turn can result in increasing respiratory muscle activity, in the respiratory muscles' fatigue, and their less co-ordinated activity. This may be mainly reflected by the increased $\%CoV_{RCamp/ABamp}$, found in the correlational study shedding some light on the biomechanical perspective regarding breathing pattern changes in relation to the uncontrolled asthma. A healthy breathing pattern is characterised by synchronised RC and AB displacements with some degree of variation to optimise the Vt, even though the amount of such variation has not been clearly determined yet (Yuan et al. 2013). This healthy breathing pattern is the result of continual and well-coordinated respiratory muscle function to enable changes of intrathoracic pressures in each compartment of the THA. Optimisation of respiratory muscle function is governed by the frequency of neural outputs transmitted from the respiratory centre

to spinal motor neurones. Any alteration in this complex process can induce changes in the biomechanics of breathing (Euler et al. 1970; Jennett et al. 1974; Peper and Tibbetts 1994).

There is a body of evidence to show that in asthma there is an increased mechanical load on inspiratory muscles due to airflow limitation and/or fixed airway obstruction during symptomatic periods of asthma (Yuan et al. 2013; Dempsey and Smith 2014). This, in turn, can result in the fatigue of inspiratory muscles, such as the diaphragm, and the supplementary activation of accessory respiratory muscles. The use of accessory respiratory muscles can lead patients to adopt an upper thoracic breathing pattern, characterised by the predominant use of the ribcage during resting breathing (Courtney et al. 2008; Courtney et al. 2011). However, a significant increase in the RC_{amp}/AB_{amp} proportions was not found in the uncontrolled asthma group of this correlational study when compared to the well-controlled asthma group. This was possible due to a potential posture effect on this examined parameter as mentioned in the previous section.

All these in line with the presence of hyperventilation in the uncontrolled asthma group of the correlational study may result not only in an upper thoracic breathing, but also in an increase of the within-individual variability of the THA movements, as were identified in this research. These can be present as a normal response to maintain the adaptability of the respiratory system during increased metabolic demands required in symptomatic periods of asthma. However, lack of comparison groups having direct measurements of respiratory muscle function in this correlational study means that potential biomechanical reasons for the increased within-individual variability of the RC_{amp}/AB_{amp} (during both respiratory phases) seen in the uncontrolled asthma group are purely speculative.

In addition, there may be psychophysiological reasons for the increased variability of breathing pattern components within uncontrolled asthma. This is based on evidence showing that psychophysiological factors, such as fear and anxiety along with an increased ventilatory drive that may accompany emotional arousal, can be important factors for altered breathing patterns in asthma (Courtney 2017). Patients with asthma are more susceptible to negative feelings, because of the higher than normal prevalence of anxiety disorders in asthma populations, especially in those with difficult-to-treat asthma who made up a significant proportion in the correlational study's sample (Vieira et al. 2011). Patients with uncontrolled asthma are more likely to have anxiety than those with well-controlled asthma (Meuret and Ritz 2010). This can further contribute to changes in breathing patterns, such as increased RR followed by changes in CO_2. This can be caused by the increased sympathetic activity during the presence of emotional arousal (Meuret and Ritz 2010).

The emotional arousal has been reported to alter breathing mechanics in healthy adults who are exposed to emotional stress (Courtney et al. 2009). The diaphragm is said to become flattened, hypertonic and relatively immobile. Feelings, such as anxiety, fear or anger, can also cause alterations in the regularity of breathing patterns (Masaoka et al. 2003: Homma and Masaoka 2008). Homma and Masaoka (2008) reported that the anxiety can contribute to an irregular RR, but no clear relationship between anxiety levels and the within-individual variability of the other examined breathing pattern components is known. In the correlational study, both well-controlled and uncontrolled asthma groups did not have significant levels of either anxiety or depression, as determined by the mean HADS scores for both domains. However, it is worth to mention that there were patients who did have increased emotional arousal and these were mainly in the uncontrolled asthma group. This can therefore support the theory that there may be psychological factors affecting the breathing pattern variability in uncontrolled asthma.

6.4.1.2 Breathing pattern components in relation to lung function

As mentioned in section 3.4.1, changes in several quantifiable breathing pattern components have been previously reported in asthma and this may be related to the variable lung function (Kesten et al. 1990; Gorini et al. 1999; Foumani et al. 2015). Factors, such as variable fixed airflow limitation or airway obstruction, can lead to the physiological or biomechanical factors regarding the increased within-individual breathing pattern variability in uncontrolled asthma. In this correlational study, the uncontrolled asthma group had decreased lung function measurements compared to the well-controlled asthma group along with significant differences in the RR and the within-individual variability of the examined breathing components. However, despite some significant correlations between a few of the examined breathing components (RR and $\%CoV_{Ti/Te}$), the $\%FEV_{1predicted}$ and the PEF, poor predictions of lung function measurements were demonstrated when either the absolute measurements or the within-individual variability of the examined breathing pattern components were used. This makes it less likely that any alterations observed in breathing patterns in this correlational study are directly associated with a change in airflow limitation or with fixed airway obstruction.

These results of the correlational study contradict some previous findings in the literature. Some authors have reported that an increased RR is associated with a relative 20% fall of the $\%FEV1_{predicted}$ during induced bronchoconstriction in asthma (Kassabian et al. 1982; Famelli et al. 1994;Gorini et al. 1999). On the other hand, other studies have showed no significant changes in both the absolute measurements and the variability of the RR, the Ti/Ttot, the %RC contribution to Vt during bronchial challenge in asthma patients (Kesten et al 1990; Stromberg and Gustafsson 1996). The changes in the absolute measurements of breathing patterns reported by Kassabian et

al. (1982) and Famelli et al. (1994) have been attributed to their use of an invasive recording method (PNT), which could have influenced the breathing pattern measurements. When both absolute measurements and variability of RR, Ti/Ttot and Vt have been examined between resting breathing and bronchial challenge using the RIP, no significant differences were reported (Kesten et al 1990; Stromberg and Gustafsson 1996).

In this correlational study, measures of the THA movements could not contribute to the significant prediction of any of the examined lung function measurements. Foumani et al. (2015) found small but significant correlations (r 0.135) between the ratio of upper third to lower third circumference of the chest wall and FEV_1 and FEV_1/FVC in 378 asthmatic patients with varying asthma control. Although measurements of the THA were obtained via an ordinary tape measure, similar findings were found in previous work of the same authors using more valid recording methods, such as chest X-rays (Foumani et al. 2014). Since Foumani et al. (2015) used different methods to monitor the THA movements compared to this correlational study, this could be speculated to have contributed to these contradictory findings. Beside this, these contradictory findings may be due to the position in which recordings were taken even though the position, in which Foumani et al. (2015) took measurements, was not reported.

In this correlational study, firm conclusions about the ability of the examined breathing pattern components to predict lung function measurements cannot be drawn despite identifying a correlation between only two breathing pattern components (RR and $\%CoV_{Ti/Te}$), $\%FEV_{1predicted}$ and PEF. This is mainly because of the limited variance in lung function measurements observed among the studied patients of the correlational study. Therefore, the regression results regarding predictions of lung function measurements should be interpreted with caution. Only 42 out of 122 patients had 20% less than $\%FEV1_{predicted}$ and only 28 out of 122 patients had FEV_1/FVC <0.70. These were mainly patients with moderate-to-severe and uncontrolled asthma. This limited variance in obtained lung function measurements means that regression results could be biased, as reflected by the presence of large SE and 95%CI for beta coefficients of breathing pattern components. So this leads to no firm conclusions about the use of breathing pattern components to predict lung function in asthma.

6.4.1.3 Associations between breathing pattern components and asthma-related quality of life

Although firm conclusions cannot be drawn from this correlational study regarding the use of breathing pattern components as a surrogate marker for lung function in asthma, quantifiable breathing pattern components were found to be associated with asthma-related quality of life. In the asthma literature, it is has been reported that patients with uncontrolled asthma have lower

quality of life scores, often in association with DB (Hagman et al. 2007; Agache et al. 2012; Denton et al. 2018). This has been mainly determined by examining the associations between the AQLQ and the NQ (Agache et al. 2012; Courtney 2017; Ok et al. 2018). To the best of the researcher's knowledge, only one recent study by Denton et al. (2019) examined characteristics of several components of breathing patterns in association with asthma patients' quality of life. The authors reported that patients with low quality of life scores had not only an increased NQ score, but also breathed with thoracic dominance characterised by an increased RR. However, in the authors' study, a specialist respiratory physiotherapist evaluated both the thoracic dominance and the increased RR subjectively through observational methods.

In comparison to Denton et al. (2019), the correlational study used a validated non-invasive monitoring tool to quantify specific components of breathing patterns in patients with asthma. The correlational study secondary found that the RR was a significant predictor of poor asthma-related quality of life, confirming the results reported by Denton et al. (2019). In addition, this correlational study goes further by suggesting that the within-individual variability of the RR, the Ti/Te and the RC_{amp}/AB_{amp} are associated with lower mini-AQLQ scores asthma. This, in turn, highlights the potential impact of a well-controlled stable breathing pattern on patients' quality of life, suggesting that breathing pattern variability can be considered as a surrogate marker of quality of life.

6.4.2 The use of the breathing pattern components to secondary characterise dysfunctional breathing in asthma

Another secondary aim of this correlational study was to examine the use of timing parameters and the THA movements as a surrogate marker of the presence of DB in an asthma population. As mentioned in section 3.4, the DB is a multidimensional term to describe several disturbances in breathing functionality and has been determined to be a common coexisting problem in asthma (Stanton et al. 2008; Baker and Everard 2015, Boulding et al. 2016). It encompasses a wide spectrum of common breathing abnormalities, with the most commonly reported respiratory symptoms being the increased RR, the predominant RC motion during resting breathing, the shortness of breath, the frequent sighing and wheezing (Courtney et al. 2008;Baker and Everard 2015; Boulding et al. 2016; Courtney 2017). To date, monitoring DB has been based on subjective questionnaires, such as the NQ, which has been reported to be associated with uncontrolled asthma (Agache et al. 2012; Veidal et al. 2017). However, only a limited number of quantifiable breathing pattern components have been examined in relation to the presence of DB.

Courtney et al. (2011) investigated whether greater RC motion than AB motion was associated with higher NQ scores during resting breathing in sitting position. The THA movements were assessed using the MARM in 84 self-referred or clinical practitioner referred adults with concerns about their breathing. The authors found weak correlations (r 0.08) between the upper RC contribution to the total breathing motion and the NQ scores. In this correlational study, absolute measurements of the RR and the within-individual variability of the examined breathing components were found to be associated with the NQ scores. An increased RR was found to be a significant predictor of the presence of DB, but a linear relationship between these variables could not be generalised. According to the correlational study's results, it was possible to have a high RR, but no DB or to have a low RR, yet still have DB. Courtney et al. (2011) has previously reported altered breathing patterns as measured via the NQ in the absence of hyperventilation as measured by the levels of CO_2. However, direct measurements of CO_2 were not obtained in this correlational study, so it is not possible to confirm the non-linear relationship between the RR and the presence of DB.

On the other hand, the relationship between the within-individual variability of the examined breathing components and the NQ was found to be linear. Patients with NQ ≥10 were found to have significantly increased $\%CoV_{RR}$, $\%CoV_{Ti/Te}$ and $\%CoV_{RCamp/ABamp}$ (during both respiratory phases) compared to those with NQ <10. The within-individual variability of the examined breathing components could predict presence of DB, with these predictors accounting for 25% of the probability of DB being present. Also the within-individual variability of the examined breathing pattern components was found to be a good classifier for the presence of DB. However, based on the individual ROCs and AUC of the examined breathing components, the $\%CoV_{RR}$ and $\%CoV_{Ti/Te}$ were found to be better indicators than using the $\%COV_{RCamp/ABamp}$.

These findings are dependent on the use of the NQ for monitoring presence of DB. This questionnaire has been criticised within the asthma literature, even though it is commonly used to detect DB in clinical practice (Vidotto et al. 2019). The NQ was initially designed to detect hyperventilation (Dixhoorn and Duivenvoorden 1985), but it is now frequently used to determine the presence of DB characterised by a range of both respiratory and non-respiratory signs (Baker and Everard 2015). Hyperventilation is a specific metabolic response that is not considered as an absolute discrete entity within all patients with DB, and yet many of the symptoms included in this questionnaire have been reported to be observed in DB (Gardner 2004). Although frequently used in asthma studies, only one study by Grammatopoulou et al. (2014) has previously validated its use in individuals with hyperventilation secondary to asthma.

One of the creators of this questionnaire has revised his initial ideas and now believes that the NQ mainly reflects the subjective psychic dimension of breathing (Dixhoorn and Folgering 2015). These authors suggest that since breathing is multidimensional, multicomponent assessment is recommended. Such assessments should include ventilatory parameters and breathing pattern parameters in line with subjective variables, such as the NQ. This correlational study showed that some of the breathing pattern components, which can be used to characterise DB, are the within-individual variability of the RR, the Ti/Te and the RC_{amp}/AB_{amp} (during both respiratory phases).

On the other hand, the use of the within-individual variability of the examined breathing pattern components were found to leave more unexplained variance for predicting presence of DB than what was estimated for asthma control. This could be not only due to the method used for identifying presence of DB, but also due to the selected NQ cut-off point for patients' classification into the studied groups. In clinical practice, a NQ score >23 is used to indicate DB (Baker and Everard 2015; Boulding et al. 2016). However, lower scores do not exclude the possibility of DB being present (Grammatopoulou et al. 2014; Dixhoorn and Folgering 2015).

In the correlational study, the researcher wanted to have certainty that those classified, as having no DB, genuinely had no DB. Since individuals with an NQ >10 might still show mild hyperventilation (Dixhoorn and Hoefman 1985; Thomas et al. 2005), a cut-off point <10 was used to define asthma patients with no DB. However, in the study's sample, there were NQ scores between 10 and 17 points (n=21) and 5% of these cases were found as influential cases of the applied regression model. This could have caused unexplained variance in the measurements of the predictors used in the initial regression model including the within-individual variability of the examined breathing pattern components. When these cases were excluded, better ROC curves and percentages of sensitivity and specificity were obtained, especially for $\%CoV_{RCamp/ABamp}$. Based on the above, this correlational study suggests that the within-individual variability of the examined breathing components can be considered as a surrogate physiological marker for the presence of DB.

6.5 The limitations of the correlational study

In the correlational study, medium association between the within-individual variability of the examined breathing components and asthma control was found. Identification of a stronger relationship may have not been possible. This is not only because of the selected study design being prone to confounding factors, as discussed in more detail in section 8.3. This is also due to the looking at the association between subjective patient-related outcomes and an objective physiological measurement of breathing. The assessment of asthma control was based on the

patients' perception about their asthma irrespective of the use of a valid and reliable questionnaire. Their opinion could have been influenced by their complexity of their medical condition without changes in physiological markers being present. Patients with asthma, especially those having severe asthma, are likely to have poor perception of what constitutes well-controlled asthma due to the complexity of their medical condition (Menzies-Gow and Chiu 2017). This may be due to presence of psychological factors, which can contribute to the patients' misinterpretation of their asthma control and cause potential discordance with objective physiological markers or the lack of strong associations between them (Baiardini et al 2015).

In this correlational study, there was a lack of cross-validation of identified significant predictors of asthma control in large subgroups. Subgroup analysis was used to assess the maintenance of identified associations between the examined variables within male, female and moderate-to-severe asthma subgroups. Although consistency of the relationship between the examined breathing pattern components and asthma control was found in these small subgroups, larger subgroups would be preferable to perform regression analysis. This would enable the researcher to cross-validate these results rather than applying simple correlation analysis within the study subgroups.

The sample size of this study was based on rules of thumb, providing a minimum sample for applying different type of regression analyses. Although adequate sample was obtained to address the primary and some of the secondary aims of this correlation study, limited variance in lung function measurements was obtained. This raised concerns about the trustworthiness of multiple linear regression results regarding predictions of lung function measurements. Thus, a larger sample would be required for looking at associations between these variables.

A last limitation of this correlational study is that maintenance of the associations between the examined breathing pattern components and asthma-related variables over time cannot be guaranteed due to the selected study design. This is further discussed in the section 8.3. However, it is acknowledged that in the future an observational longitudinal study is required to explore the maintenance of the identified associations seen in this correlational study.

6.6 Summary of the correlational study

This correlational study used a previously validated non-invasive recording method (SLP) to measure specific quantifiable components of breathing patterns, such as timing parameters and a parameter associated with the THA movements, in adults with different asthma severity and asthma control. It was found that the within-individual variability of the RR, the Ti/Te and the RC_{amp}/AB_{amp} (during both respiratory phases) can predict asthma control as measured on a single

occasion. On the other hand, absolute measurements of these breathing pattern components could not predict asthma control, even though only absolute measurements of the RR was found to be a significant predictor of asthma control. The within-individual variability of the above breathing components could secondary predict possible presence of DB and low scores of mini-AQLQ scores. However, no firm conclusions could be drawn regarding predictions of lung function via the use of the examined breathing pattern components (absolute measurements and within-individual variability).

Chapter 7 Responsiveness of breathing patterns following a physiotherapy breathing retraining programme

This chapter presents the responsiveness study conducted to provide some preliminary data regarding the ability of the examined breathing pattern components to respond to a specific adjunctive asthma treatment. This was a clinical physiotherapy breathing retraining programme, specifically designed to modify breathing patterns. Although breathing retraining is recommended in current evidence-based guidelines (GINA 2018), there is little body of evidence examining any effect of this intervention on the examined breathing pattern components of this research (see Chapter 3, section 3.6). In the same chapter, an individual discussion of the findings is provided prior to a combined discussion of the key findings of this research as provided in the next chapter.

The responsiveness study was originally set up by the researcher's primary supervisor (Prof Anne Bruton). This study was to characterise breathing patterns during resting breathing and speech breathing before and after a clinical physiotherapy breathing retraining programme. Due to changes in personnel, the responsiveness study was handed over to the researcher, who collected and analysed the data according to the needs of this research. The responsiveness study was never completed as planned for reasons given in section 7.2.5, so that only 6 patients with moderate-to-severe asthma were recruited. However, these data were deemed appropriate to provide additional results of this thesis exploring the use of breathing patterns as physiological marker in asthma management.

7.1 Aims and objectives of the responsiveness study

Collecting breathing pattern data before and after a clinical physiotherapy breathing retraining programme from a small asthma population aimed to provide preliminary data of changes in the examined breathing pattern components of this research after this intervention. An initial secondary aim was to observe potential associations between potential changes in the examined breathing components and patient-related outcomes, following the breathing retraining programme. This could initially support any associations identified in the correlational study over time.

The objectives of this research were:

1) To record breathing pattern components (as examined in the correlational study) before and after face-to-face physiotherapy breathing retraining sessions at several time points, during resting breathing.
2) To obtain data relating to asthma control, presence of DB, asthma-related quality of life, and lung function measurements before and after face-to-face physiotherapy breathing retraining sessions at several time points.

The same tools that were used in the correlational study, were also applied in the responsiveness study (see sections 6.2.6.2, 6.2.6.3, 6.2.6.4).

7.1.1 Research question

The primary research question was: Do specific quantifiable components of breathing patterns change before and after breathing retraining programme?

A sub-research question was: Are changes in specific quantifiable components of breathing patterns correlated with any respective changes in patient-related outcomes after breathing retraining programme?

The primary research hypothesis was that the examined breathing pattern components would significantly differ between baseline and after breathing retraining programme. A decrease in the RR characterised by longer Te than Ti and an increase in the AB_{amp} after breathing retraining was expected. Also a decrease in the within-individual variability of these breathing pattern components after breathing retraining was hypothesised. Changes in the examined breathing components were also hypothesised to be related with improvements in patient-related outcomes.

7.2 The methods of the responsiveness study

7.2.1 Study design

This was a test-retest repeated measures single-arm (uncontrolled) design involving adult patients with a diagnosis of asthma who were referred for breathing retraining in the University Hospital Southampton (UHS). Breathing retraining was implemented by a specialist respiratory physiotherapist in the UHS. The examined breathing components were recorded using the SLP for 5 minutes during several recording sessions before and after breathing retraining.

7.2.2 Settings and ethical considerations

Willing adult patients with asthma, who had been referred for breathing retraining, were invited to attend a baseline measurement recording session in the physiology laboratory within the Wellcome Trust Research Facility at UHS (see section7.2.6). Patient recruitment was performed via the respiratory centre at the UHS (see section 7.2.5). Ethical approval (IRAS ID: 197059; REC reference: 16/SC/0083) (see Appendix B) was given in June 2016 and the ongoing study was closed (incomplete) in April 2018 after being extended for one year beyond the initial planned end date.

7.2.3 Participants' selection

Eligible participants for this study were those who were adult patients (aged 18 years or over) with a clinical diagnosis of asthma receiving asthma treatment according to the GINA guidelines (2016), and had been referred for a physiotherapy breathing retraining programme at the UHS. The patients' referrals for face-to-face breathing retraining sessions were made by respiratory specialists in the outpatient asthma clinics at the UHS. Patients who were unwilling to give an informed consent and those taking part in any other study involving a clinical intervention were excluded.

7.2.4 Sample size

Due to a lack of normative data about clinically important differences in the examined breathing pattern components after breathing retraining, no formal power calculations were conducted based on these breathing pattern measurements. A sample of 48 patients with asthma had been determined to be the minimum sample size required. This was based on the known clinically important difference for the asthma quality of life scale (AQLQ). The minimum clinically important difference of the AQLQ has been reported to be 0.5 (Thomas et al. 2009). Given this information, the minimum sample needed to demonstrate a difference in the AQLQ of 0.5 or greater, with 90% power and a type I error rate of 5%, was 48. To allow for up to 30% attrition (for example non-attendance of patients to breathing retraining sessions), as had been reported to occur by the specialist physiotherapist, a convenient total sample of 72 patients was suggested.

After the researcher took over the responsiveness study, an additional estimation of an adequate sample size was performed to meet the secondary aim of this research. This was to look for correlations between any changes in the examined breathing pattern components and patient-related outcomes following breathing retraining. Moinester and Gottfried (2014) have proposed several minimum sample sizes based on a given strength of a bivariate correlation between

variables (r), a selected significance level (a) and suggested width of 95% CI (w). According to the tables provided by Moinester and Gottfried (2014) a minimum sample size of 56 patients was re-estimated, with r 0.80, a 0.05 and w 0.10.

7.2.5 The participants' recruitment procedure

Volunteer patients were invited to take part in the study using an information pack (see Appendix B). This was sent to the patient's home address with their first appointment letter for a face-to-face breathing retraining session. These were sent through the respiratory centre administrative team of the UHS. The information pack contained an invitation letter, the PIS and a reply form. Patients who were interested in taking part in this research were advised to complete the reply form with their contact details and post to the researcher using the pre-paid, pre-addressed envelopes. They could directly contact researcher via email or work phone number. Upon contact, the patients' eligibility was evaluated and if they met the study's eligibility criteria, they were invited to a baseline measurement prior to their first breathing retraining session with the specialist respiratory physiotherapist.

On average, 10 information packs were sent to potential participants per month, from September 2016 to December 2016, and from February 2018 to March 2018, as reported by the specialist respiratory physiotherapist. The specialist respiratory physiotherapist was responsible for the distribution of information packs to the respiratory centre administrative team. The figure below provides a summary of the recruitment process. Only 6 patients were finally recruited between September 2016 and March 2018. Patients' recruitment started in September 2016, but stopped in January 2017 due to the specialist physiotherapist taking one year maternity leave. No other physiotherapists were available to take over her clinical caseload, so the ongoing study was put on hold during her absence and an extension was granted by the Ethics committee. The physiotherapist returned to work in January 2018 and the study restarted in February 2018 with a few new patients being enrolled in the study. However, the specialist respiratory physiotherapist then resigned from her position and no replacement was immediately appointed. There was considerable uncertainty over how long it would take for any replacement physiotherapist to be appointed, so in March 2018 the decision was taken to close the study

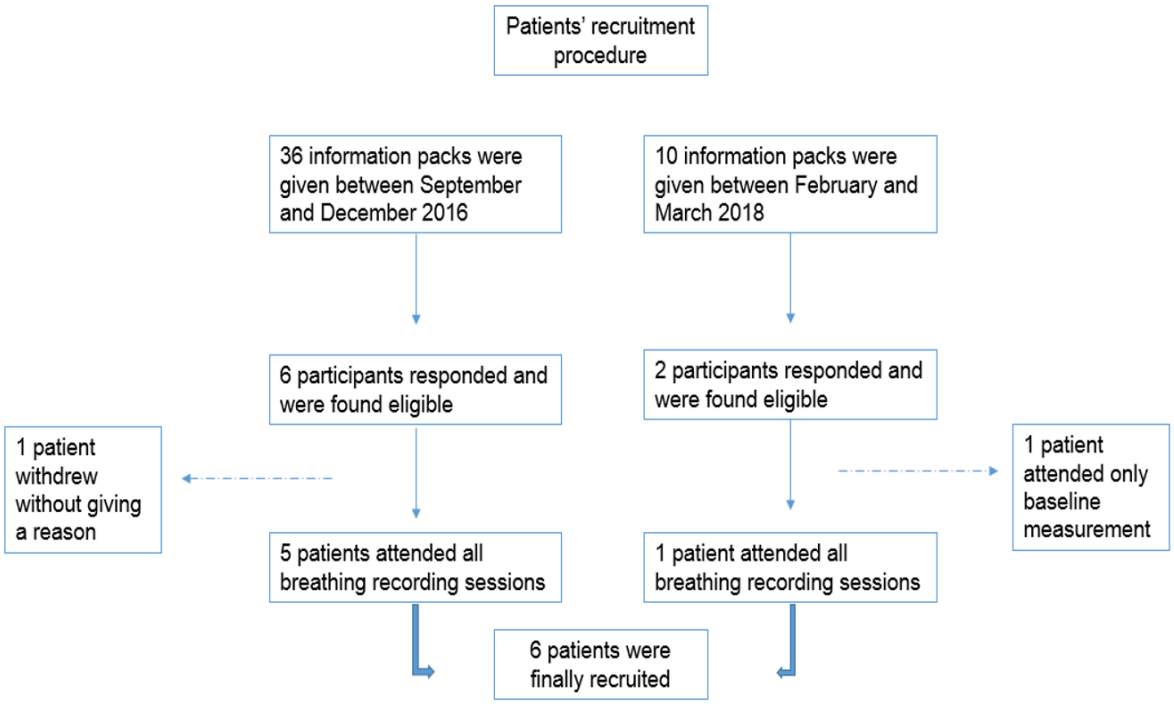


Figure 7-1: The flowchart of participants' recruitment process

7.2.6 The research schedule of breathing pattern recording sessions in accordance with the breathing retraining sessions

The participants were invited to attend three recording sessions (see Figure 7-2). To minimise patient burden, each recording session was planned to take place on the same day as their breathing retraining sessions. They were carried out one hour prior to the 1st, 2nd and 4th patients' clinical appointment for breathing retraining session. The total number of breathing retraining sessions provided to adult asthma outpatients at the UHS is usually tailored to the individuals' clinical needs. It ranges from 1 to 10 sessions for up to one year. On average, patients receive 4 breathing retraining sessions over 6 months. Only breathing pattern data collected from patients receiving a minimum of 4 breathing retraining sessions were kept and analysed for the purposes of this responsiveness study. The time between the baseline measurement and the 2nd recording session ranged from 2 to 6 weeks among the 6 participants enrolled into this research. The time between the 2nd and the 3rd recording session ranged from 4 to 9 weeks.

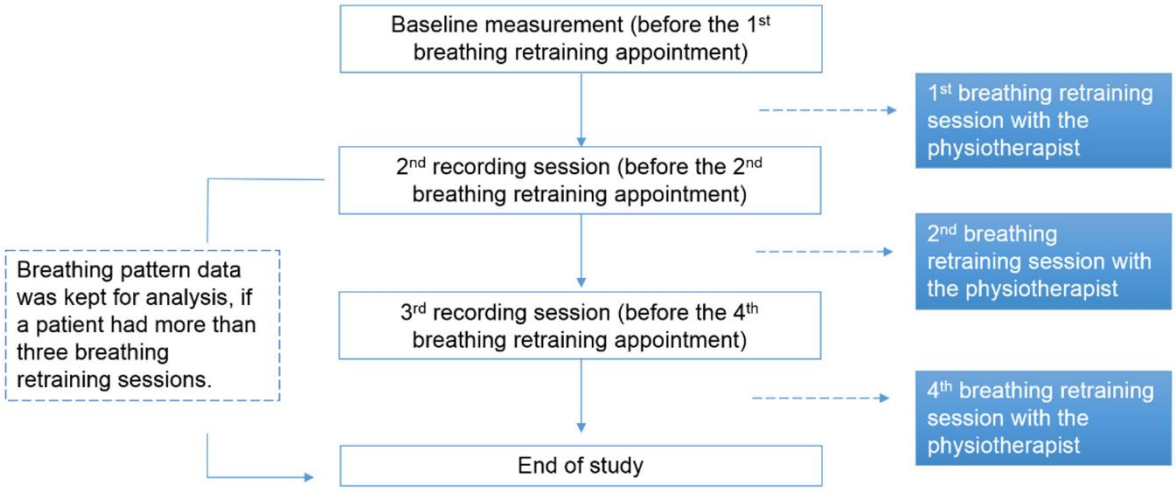


Figure 7-2: The flowchart of the sequence of the recording sessions in accordance with the breathing retraining sessions

7.2.7 The physiotherapy face-to-face breathing retraining sessions

The total time between the 1st and 4th breathing retraining session ranged from 8 to 14 weeks among the 6 participants. This was not only because of participant availability, but also to the availability of appointments for a face-to-face session with the specialist respiratory physiotherapist in the UHS. Each breathing retraining session lasted a minimum of 30 minutes, but was adjusted to the patients' needs. The content of the breathing retraining sessions was similar to the programme published by Thomas and Bruton (2014). The breathing retraining programme included both instructional and practical phases. The specialist respiratory physiotherapist aimed to normalise breathing patterns by adopting a slower RR by prolonging expiration phase and reducing overall minute ventilation. Patients were taught to use the abdomen rather than the upper thoracic area during resting breathing. Nasal breathing rather than mouth breathing was encouraged and patients were taught relaxation techniques. As mentioned in section 2.3.1, the rationale behind these techniques is based on addressing signs of DB in asthma.

During the 1st breathing retraining session, the physiotherapist informed patients about asthma and how it can affect their breathing. The potential effects of the DB on asthma symptoms and the potential benefits of breathing retraining on their clinical condition were explained. Then there was an instructional phase teaching patients to perform slow nasal abdominal breathing. After the instructional phase, patients practiced individually each component of this technique (slow nasal breathing, abdominal breathing) and then put them together. The time for practicing varied between 10 and 15 minutes according to the patients' needs. The patients were advised to practice twice daily at home and steadily to increase the amount of time spent practicing.

During the 2nd breathing retraining session, a review of the patients' progress was performed. The patients were asked to demonstrate their breathing techniques so that the physiotherapist could provide constructive feedback. In this session, the physiotherapist added teaching about controlled breath holds at the end of expiration during normal resting breathing. Breaths were hold until patients felt the need to breathe. She also aimed to teach patients to adopt a stable pace of breathing whilst applying breathing techniques. The patients were advised to practice slow abdominal breathing control exercises three times per day in a sitting position.

In the 3rd breathing recording session, progress was reviewed and any problems discussed. This session was mainly to reinforce or improve on techniques not mastered in the 2nd breathing retraining session. Additionally, practicing all the above breathing techniques was performed in other positions, such as standing. Finally, patients were advised to practice breathing techniques 2 times per day during normal activities, such as walking.

7.2.8 Equipment used for data collection

The tools and equipment used in the responsiveness study were the same as those used in the correlational study (see section 6.2.6). A brief overview of the tools used in this research is provided below.

A case report form (see Appendix B) was used to obtain the participants' demographic data (gender, age, BMI) and their medication usage during baseline measurement. Case report forms for the 2nd and 3rd recording session (see Appendix B) were also used to obtain data regarding any potential change of the patients' medication usage and their health status among the three recording sessions.

Asthma related outcomes such as asthma control, the presence of DB and patients' quality of life were obtained in all recording sessions via the ACQ, the NQ and the mini-AQLQ respectively. The patients' levels of anxiety and depression were checked via the patients' self-assessment using the HADS questionnaire.

In addition to the above measurements, recordings of breathing components of interest were obtained via the SLP and the data managed as for the earlier studies of this research. The same calibrated portable spirometer was used to obtain $\%FEV_{1predicted}$, FEV_1/FVC and PEF among the three recording sessions.

7.2.8.1 Data collection procedure

The following flowchart summarises the data collection procedure of this research. The same sequence of events was followed in all recording sessions except that demographic data were collected only at baseline measurement. Recordings of quantifiable components of breathing patterns during resting breathing were performed as described previously (see section6.2.7). Lung function tests were performed according to published guidelines set out by Miller et al. (2005) and a detailed description has been previously provided in section 6.2.7.

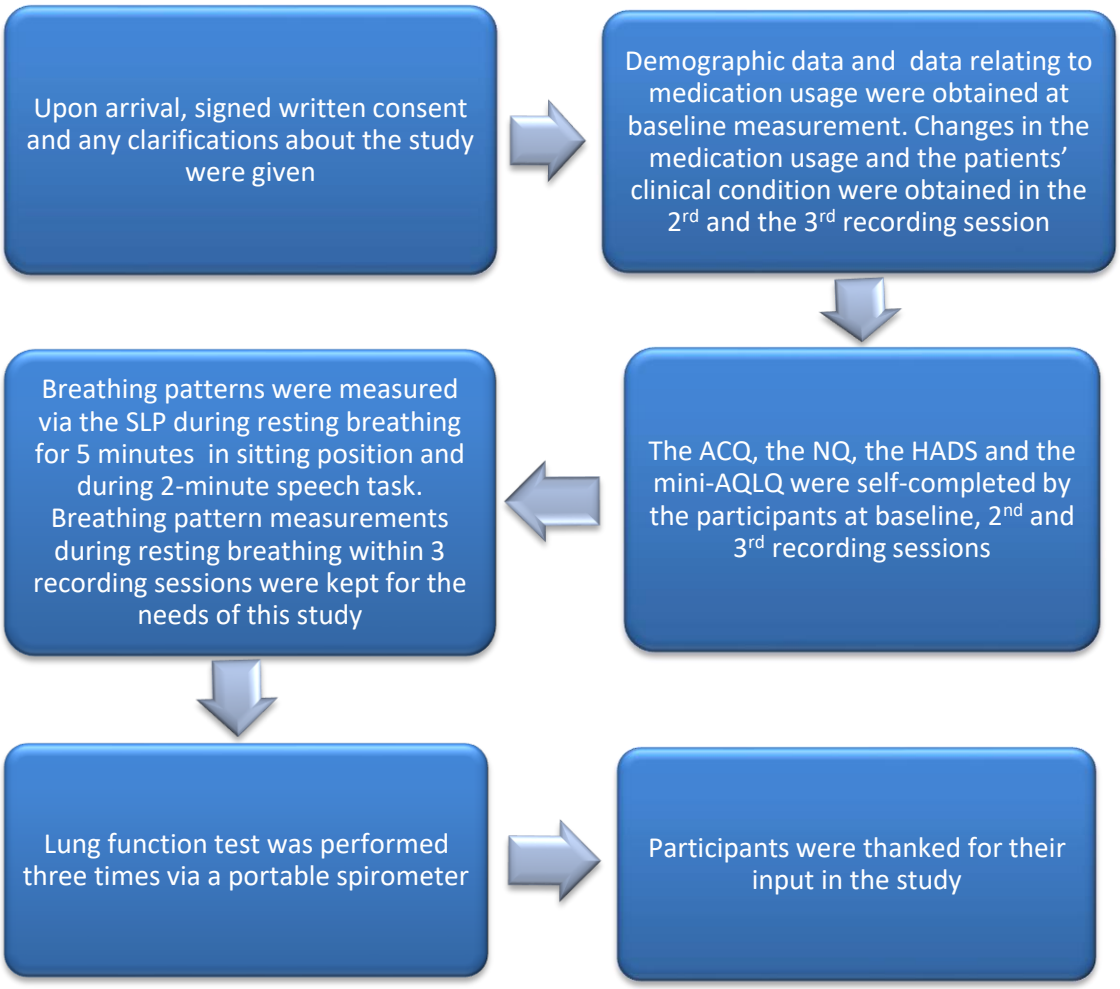


Figure 7-3: The flowchart of the sequence of events during the data collection procedure among the 3 recording sessions

7.2.8.2 Extraction of the examined breathing components

Appraisal of the quality of the SLP data and extraction of the breathing pattern data was performed as described in section 6.2.8, performing a breath-by-breath analysis. Parameterised data of both absolute values and %CoV of the RR, the Ti/Te and the RC_{amp}/AB_{amp} (during both

respiratory phases) were calculated for each individual at baseline and follow-ups. The obtained values of these variables were used for descriptive statistical analysis.

7.2.9 Descriptive analysis of the obtained quantitative data

Due to the very small sample size recruited (n=6), the original statistical analysis plan could not be implemented. It was not deemed meaningful to perform a statistical analysis based on group mean values of examined breathing components and asthma-related outcomes for making comparisons between baseline and follow-ups. Correlational analysis could also not be performed to look at potential relationships between the changes of the examined breathing components and the examined asthma-related outcomes within the group over time.

All the collected data regarding the examined breathing pattern components and asthma-related outcomes were analysed individually, using descriptive statistics between baseline and follow-ups for each participant enrolled in this responsiveness study. This was to provide some preliminary proof-of-principle data to see if there was any pattern of response to breathing retraining.

7.3 The results of the responsiveness study

7.3.1 Demographic data of patients

In total, 6 adult patients with asthma were recruited. From those, 3 were females and the study's sample age ranged between 36 and 70 years old. The Table 7-1 provides an overview of the demographic data for each participant at baseline measurement. From the total sample, 4 participants had BMI >30 kg/m^2, whereas the rest of them had high BMI (> 25 kg/m^2). Regarding patients' asthma phenotypes, 4 patients self-reported to have had a positive allergy skin test and considered to have allergic asthma. From those, their age of asthma diagnosis varied from 8 to 27 years old. On the other hand, two patients had been diagnosed with non-allergic asthma with their age of asthma diagnosis being 68 and 20 years old respectively.

Table 7-1: Demographic data of the participants enrolled in the responsiveness study

Participant	Gender*	Age (years)	BMI (kg/m^2)	Asthma phenotype	Age of asthma diagnosis
1	F	48	50.29	Allergic	8
2	F	52	31.63	Allergic	15
3	F	55	35.32	Allergic	13
4	M	70	27.46	Non-Allergic	68
5	M	36	32.65	Non-allergic	20
6	F	54	26.57	Allergic	27

***F**: female; **M**: male

7.3.2 Asthma medication usage, health status and emotional status of participants among the three recording sessions

Complete data from all the participants within the three recording sessions were obtained. Five of the participants had severe asthma with only 1 participant having moderate asthma (participant 6, see Table 7-4). All studied patients underwent a minimum of 3 breathing retraining sessions with the period of time between baseline measurement and the 3rd recording session varying from 8 to 14 weeks (see Table 7-4). At baseline measurement, 5 out of 6 patients presented with anxiety ($HADS_{anxiety}$ >8) and 4 out of 6 patients had depression ($HADS_{depression}$ >8). At the end of this responsiveness study, no distinct pattern in changes to anxiety and depression scores could be seen (see Table 7-2).

In overall, 4 out of 6 participants had no changes in controller medication between the baseline measurement and the 2nd follow-up (see Table 7-4). From those, 3 participants also had no change in controller medication at the 3rd follow-up. In the total sample, one participant increased controller medication between baseline and the 2nd recording session due to asthma worsening. However, the clinical condition of this participant remained stable by the end of the study and he self-reported a decrease in ICS (2 puffs less a day). The health status of only one participant was unstable across all the recording sessions. This participant experienced a chest infection and skin allergy prior to the 2nd and 3rd recording sessions respectively.

Decrease in use of short acting $beta_2$ agonists (SABA) was found in 5 out of 6 participants between the 1st and 3rd recording session, even though none of the participants stopped using the SABA medication (see Table 7-3). Three out of 6 participants reported a decrease in the SABA use between the baseline and the 2nd recording session. From those, only two participants reported a further decrease in the SABA use between the 2nd and the 3rd recording session. From those who

did not reduce the SABA use (n=3) between the 1st and the 2nd recording session, 2 participants reported a decrease in the SABA use at the end of the responsiveness study (see Table 7-3).

Table 7-2: The results of emotional arousal (anxiety and depression) for each participant during the three recording sessions

	1st recording session		2nd recording session		3rd recording session	
Participant	***HADS (A)**	***HADS (D)**	**HADS (A)**	**HADS (D)**	**HADS (A)**	**HADS (D)**
1	x	✓	x	x	x	x
2	✓	✓	✓	✓	✓	✓
3	✓	✓	x	✓	✓	✓
4	✓	✓	✓	✓	x	✓
5	✓	x	✓	✓	✓	✓
6	✓	x	✓	x	✓	x

✓ shows presence of anxiety or depression (HADS≥8 for each domain); x shows absence of anxiety or depression (HADS<8 for each domain); ***HADS(A):** anxiety domain; **HADS(D):** depression domain

Table 7-3: Summary of the rescue medication usage (SABA) for each participant among the three recording sessions

Participant	**1st session**	**2nd session**	**3rd session**
1	5-8 puffs*	3-4 puffs	1-2 puffs
2	13-16 puffs	5-8 puffs	5-8 puffs
3	>16 puffs	13-16 puffs	3-4 puffs
4	>16 puffs	>16 puffs	3-4 puffs
5	13-16 puffs	13-16 puffs	3-4 puffs
6	5-8 puffs	5-8 puffs	5-8 puffs

*the number of puffs was obtained from the ACQ_{7item}

Table 7-4: Summary of the controller medication usage and the participants' health status among the three recording sessions

	1st recording session	2nd recording session		3rd recording session		Study duration*
Participant	**Controller medication**	**Health status**	**Controller medication**	**Health status**	**Controller medication**	
1	Medium doses of ICS (6 puffs per day) Tiotropium (2 puffs twice a day),	Stable	No change	Stable	No change	11 weeks
2	High doses of ICS (6 puffs a day),	Chest infection 2 weeks prior session	Antibiotics were added	Skin allergy Chest infection 2 weeks prior session	Antihistamine medication was added Antibiotics use	12 weeks
3	Medium doses of ICS (6 puffs per day) Tiotropium use (2 puffs twice a day),	Stable	No Change	Stable	No change	13 weeks
4	Medium doses of ICS (4 puffs per day) LABA (4 puffs per day)	Asthma exacerbation	Add Tiotropium (2 puffs per day)	Stable	ICS reduced per 2 puffs a day	14 weeks
5	Medium doses of ICS (4 puffs per day), LABA (4 puffs per day) Tiotropium (2 puffs per day)	Stable	No change	Stable	No change	12 weeks
6	Low dose of ICS (2 puffs per day) LABA use (2 puffs per day)	Stable	No change	Acute allergy	Antihistamine medication was added	8 weeks

***Study duration:** the interval time between the 1st recording session and the 3rd recording session; **ICS:** inhaled corticosteroids; **LABA:** long acting beta$_2$ agonists

7.3.3 Lung function measurements after breathing retraining

Lung function measurements among 6 participants remained relatively stable throughout the study (see from Table 7-5 to Table 7-7). At baseline, 2 participants had a decrease in the $\%FEV_{1predicted}$ > 20, but there were no signs of fixed-airway obstruction ($FEV_1/FVC < 0.70$) within any of these participants. The majority of the participants (n=5) presented with similar $\%FEV_{1predicted}$ between the baseline measurement and the 3rd recording session (see Table 7-5). However, one participant had a decrease in the $\%FEV_{1predicted}$ (9.82%), which may have been related to worsening of health status due to an acute allergy and chest infection.

Measurements of the FEV_1/FVC ratio remained similar between the baseline measurement and the 3rd recording session among the 6 participants (see Table 7-6). The highest increase in the $FEV_{1/}FVC$ between the baseline measurement and the 3rd recording session was 0.09 and this was observed for one participant. In terms of PEF measurements, 5 out of 6 participants showed a small increase in the PEF between baseline measurement and the 3rd recording session with 1 participant being presented with a small decrease in the PEF (see Table 7-7). The highest observed increase in the PEF was 0.90L/min.

Table 7-5: Obtained values of $\%FEV_{1predicted}$ for each participant among the three recording sessions

Participant	1st session	2nd session	3rd session
1	100.77	98.85	97.46
2	91.92	88.07	82.10
3	60.00	62.4	62.80
4	87.46	77.25	87.46
5	49.87	47.87	47.37
6	96.28	96.28	98.51

Table 7-6: Obtained values of FEV_1/FVC for each participant among the three recording sessions

Participant	1st session	2nd session	3rd session
1	0.81	0.87	0.83
2	0.88	0.84	0.91
3	0.76	0.73	0.72
4	0.96	0.92	0.94
5	0.79	0.99	0.88
6	0.82	0.82	0.82

Table 7-7: Obtained values of PEF (L/min) for each participant among the three recording sessions

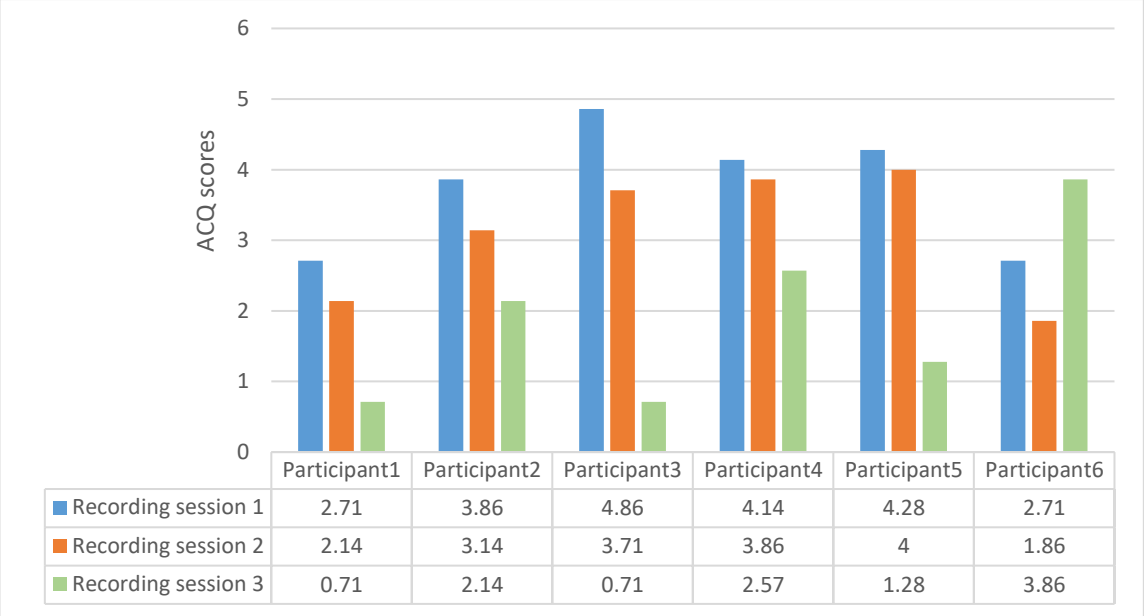
Participant	1st session	2nd session	3rd session
1	5.05	4.85	4.62
2	4.41	4.23	4.61
3	3.40	3.43	4.05
4	5.79	6.72	6.69
5	6.34	6.44	6.55
6	3.65	3.74	3.70

7.3.4 The results for patient-related outcomes involved in the responsiveness study

The Asthma Control Questionnaire

At baseline, all 6 participants had an ACQ score >1.50 indicating their asthma was uncontrolled (see Figure 7-4). At the 3rd recording session, 3 participants remained uncontrolled, 2 participants had well-controlled asthma (ACQ <0.75) and 1 participant had partially controlled asthma (ACQ 1.28). The health status of the patients with well-controlled and partially controlled asthma at the end of the study was clinically stable among all the recording sessions with no changes in the controller medication usage.

It is worth noticing that the majority of the patients (n=5) showed a decrease in the ACQ scores between the baseline and the 3rd recording session implying less frequency of asthma symptoms after the breathing retraining sessions. An increase in the ACQ scores between baseline and the 3rd recording session was found for 1 participant, which may be attributed to the worsening of her medical condition. This participant self-reported an acute allergy for which she was receiving antihistamine medication and she also showed signs of anxiety ($HADS_{anxiety}$ >8).

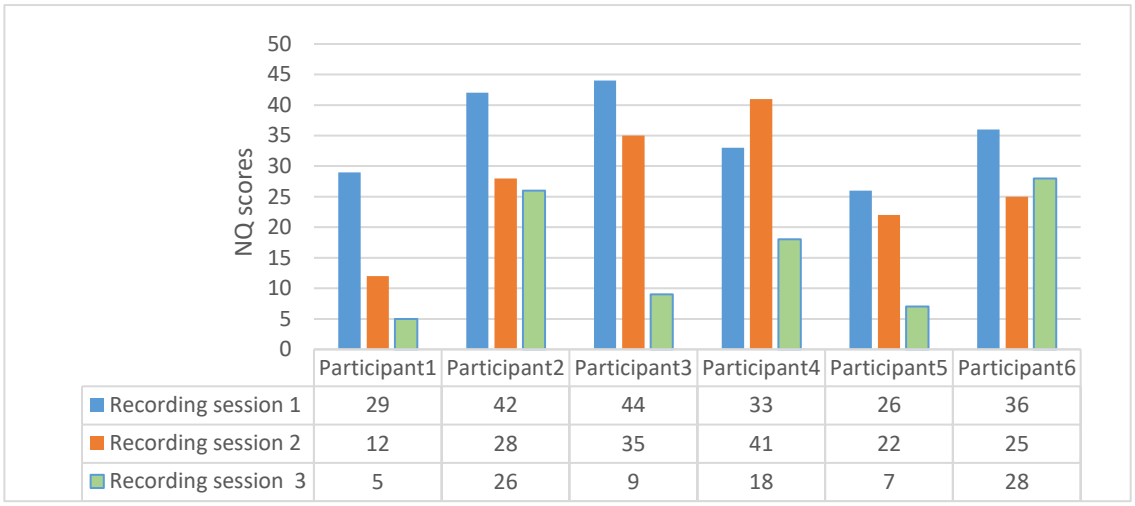


	Participant1	Participant2	Participant3	Participant4	Participant5	Participant6
Recording session 1	2.71	3.86	4.86	4.14	4.28	2.71
Recording session 2	2.14	3.14	3.71	3.86	4	1.86
Recording session 3	0.71	2.14	0.71	2.57	1.28	3.86

Figure 7-4: The ACQ scores for each participant across the three recording sessions providing their individuals scores for each recording session.

The Nijmegen Questionnaire

In terms of the NQ scores, all the participants had raised NQ scores (>23) at baseline measurement, suggesting the presence of DB (see Figure 7-5). Five out of 6 participants had raised NQ scores at the 2nd recording session. At the 3rd recording session, 3 of the participants had NQ scores < 10. The participants with NQ scores <10 at the 3rd recording session were those with well controlled (ACQ <0.75) and partially controlled asthma (ACQ 1.28).

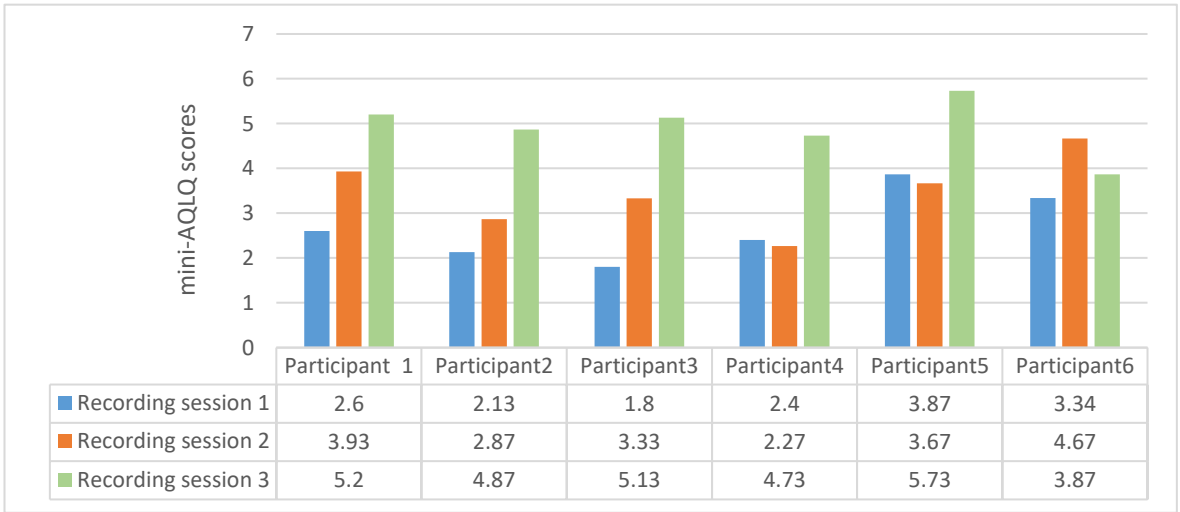


	Participant1	Participant2	Participant3	Participant4	Participant5	Participant6
Recording session 1	29	42	44	33	26	36
Recording session 2	12	28	35	41	22	25
Recording session 3	5	26	9	18	7	28

Figure 7-5: The NQ scores for each participant across the three recording sessions providing their individual scores for each recording session

The mini-Asthma Quality of Life Questionnaire

All participants had low mini-AQLQ scores at baseline measurement, suggesting poor quality of life (see Figure 7-6). The minimum and maximum scores of mini-AQLQ were 1.8 and 3.87 respectively. Individual comparisons in mini-AQLQ scores between baseline and the 3rd recording session showed an overall increase ≥0.5 in mini-AQLQ scores for all participants. The majority of participants (n=5) had an increase >2.33 in mini-AQLQ scores at the 3rd recording session showing a tendency towards improvement of participants' quality of life after breathing retraining.



	Participant 1	Participant2	Participant3	Participant4	Participant5	Participant6
Recording session 1	2.6	2.13	1.8	2.4	3.87	3.34
Recording session 2	3.93	2.87	3.33	2.27	3.67	4.67
Recording session 3	5.2	4.87	5.13	4.73	5.73	3.87

Figure 7-6: The mini-AQLQ scores for each participant across the three recording sessions providing their individuals scores for each recording session

7.3.5 Responsiveness of absolute measurements of the examined breathing components following breathing retraining sessions

The Table 7-8 provides the participants' individual mean values of RR, Ti/Te and $RC_{ampinsp}/AB_{ampinsp}$ during the three recording sessions. To avoid repetition of results regarding the RC_{amp}/AB_{amp} during both respiratory phases (inspiration and expiration), only the $RC_{ampinsp}/AB_{ampinsp}$ results are in the main text. The results for the RC_{ampexp}/AB_{ampexp} are provided in Appendix C. The Figure 7-7 shows the diagrams (a, b and c) which illustrate changes in each examined breathing pattern component for each participant during the three recording sessions.

No consistent pattern of a change in RR was observed within all participants, with some increasing, some decreasing, and some staying relatively the same. At baseline, 4 participants had RR >15 bpm. From those, 3 participants showed a decrease in the RR between baseline and the 3rd recording session and one participant had increased RR at the 3rd recording session (participant 2, Figure 7-7a). In this instance, the increased RR could have been due to the participant's deterioration of her health condition (chest infection and acute skin allergy with both anxiety and depression). Two of 3 participants who had a decrease in the RR between baseline and the 3rd recording session, had also well controlled asthma and no presence of DB after breathing retraining. Two participants had a relatively stable RR (participant 5 and 6) compared to other participants between baseline and the 3rd recording session (see Figure 7-7a), with their differences in RR being -0.86 bpm and -1.62 bpm (see Table 7-8). Those two uncontrolled asthma participants both had either normal (12-15 bpm) or lower RR at the baseline measurement (see Table 7-8).

There was also no consistent pattern of changes in relation to inspiratory and expiratory phase length. It had been expected that there would be a trend towards increasing the length of both phases, with Te increasing more than Ti, as this is the pattern most commonly taught during breathing retraining. As can be seen from Table 7-8, however, only 2 participants showed an increase in Ti/Te from the baseline measurement to the 3rd recording session (participants 2 and 5). One of these participants (participant 5) was in a clinically stable condition across all three recording sessions having partially controlled asthma at the end of this responsiveness study. Two other participants were in a clinically stable condition throughout this responsiveness study, but one of them had relatively stable Ti/Te (participant 1, see Figure 7-7b) and the other one had a decrease in Ti/Te (participant 3, see Figure 7-7b) at the 3rd recording session. However, both of them had well controlled and no presence of DB.

In addition, 4 out of 6 participants had a decrease in the RC_{amp} over the AB_{amp} between baseline and at the end of this responsiveness study, while 2 had an increase. The largest changes in the $RC_{ampinsp}/AB_{ampinsp}$ were observed in participants with $RC_{ampinsp}/AB_{ampinsp}$ >1 (participants 1, 2, 3 and 6) at baseline measurement compared to those with $RC_{ampinsp}/AB_{ampinsp}$ <1 (participant 4 and 5) (see Figure 7-7c). From those with $RC_{ampinsp}/AB_{ampinsp}$ >1 (n=4), three participants had a decreased $RC_{ampinsp}/AB_{ampinsp}$ at the 3rd recording session (participant 1, 3 and 6), reflecting less RC motion during resting breathing, with two of them having well controlled asthma and no DB at the end of the study. However one of those had an increase in the $RC_{ampinsp}/AB_{ampinsp}$ (participant 2, see Figure 7-7c).

Table 7-8: Summary of individual mean values of the examined breathing pattern components for all participants during the three recording sessions

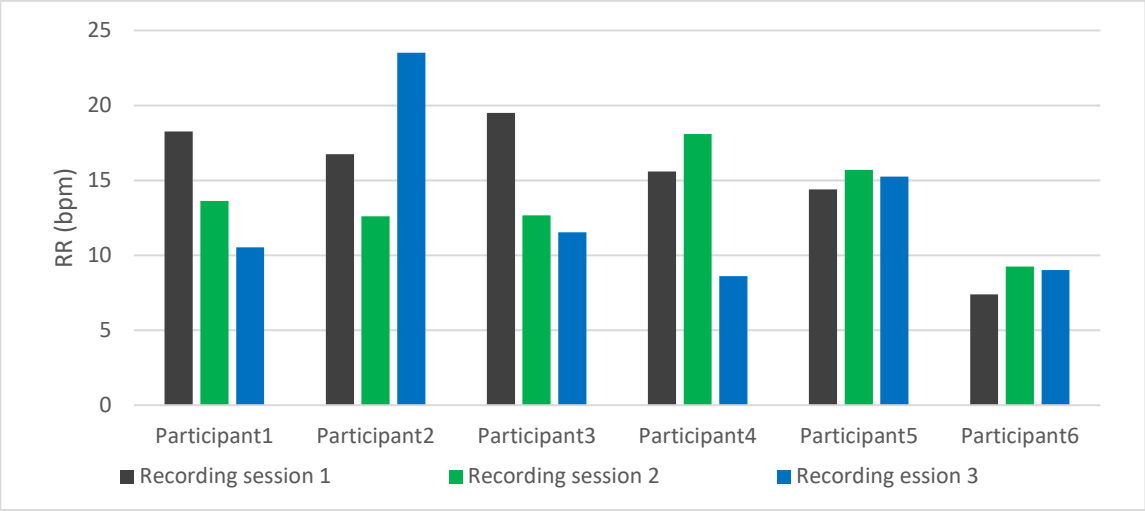
	Participant 1		Participant 2		Participant 3	
Breathing component	**μ**	**sd**	**μ**	**sd**	**μ**	**sd**
RR						
Session1	18.26 (no bc*=91)	1.30	16.74 (no bc=82)	2.79	19.51 (no bc=97)	2.88
Session2	13.63 (no bc=67)	1.82	12.60 (no bc=63)	0.55	12.66 (no bc=63)	0.55
Session3	10.53 (no bc=52)	0.45	23.52 (no bc=117)	3.58	11.53 (no bc=57)	0.55
Ti/Te						
Session1	0.64	0.22	0.87	0.29	0.76	0.23
Session2	0.69	0.24	0.64	0.13	0.57	0.09
Session3	0.65	0.13	1.02	0.40	0.54	0.08
$RC_{ampinsp}/AB_{ampinsp}$						
Session1	5.38	1.15	1.35	0.11	1.50	0.14
Session2	2.01	0.32	1.03	0.14	1.27	0.12
Session3	1.61	0.11	2.17	1.08	1.04	0.11

*number of breath cycles after performing a breath-breath analysis for each participant

Continue Table 7-8

	Participant 4		Participant 5		Participant 6	
Breathing component	**μ**	**sd**	**μ**	**sd**	**μ**	**sd**
RR (bpm)						
Session1	15.60 (no bc*=79)	1.09	14.40 (no bc=72	3.65	7.40 (no bc=37)	0.89
Session2	18.10 (no bc=90)	1.87	15.70 (no bc=78)	2.07	9.26 (no bc=46)	1.30
Session3	8.60 (no bc=43)	0.55	15.26 (no bc=76)	0.45	9.02 (no bc=45)	1.22
Ti/Te						
Session1	0.74	0.25	0.56	0.18	0.89	0.51
Session2	0.74	0.10	0.71	0.22	0.71	0.27
Session3	0.57	0.09	0.65	0.13	0.47	0.19
$RC_{ampinsp}/AB_{ampinsp}$						
Session1	0.86	0.21	0.95	0.23	2.57	0.47
Session2	0.94	0.22	0.87	0.21	1.20	0.15
Session3	1.10	0.14	0.90	0.18	1.90	0.61

*number of breath cycles after performing a breath-breath analysis for each participant



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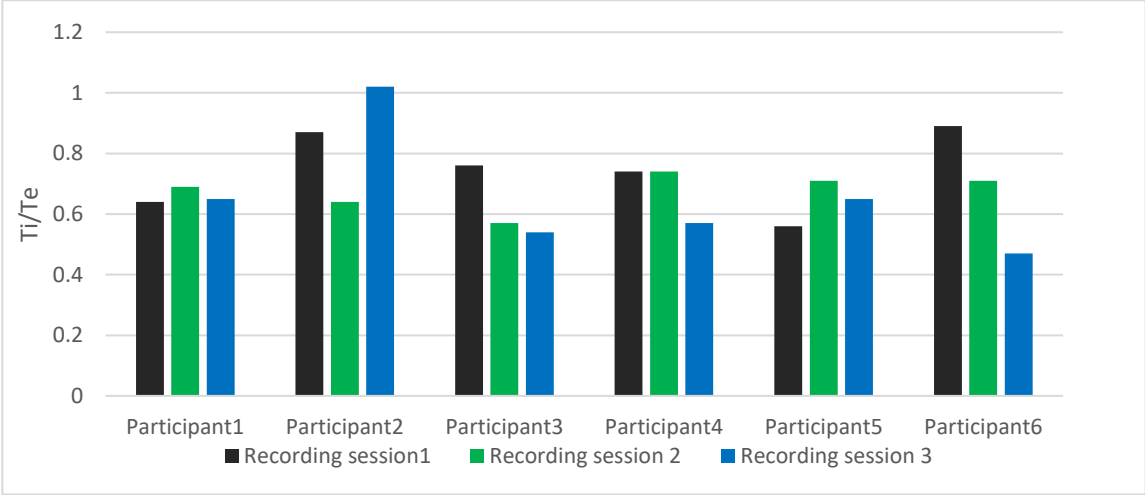

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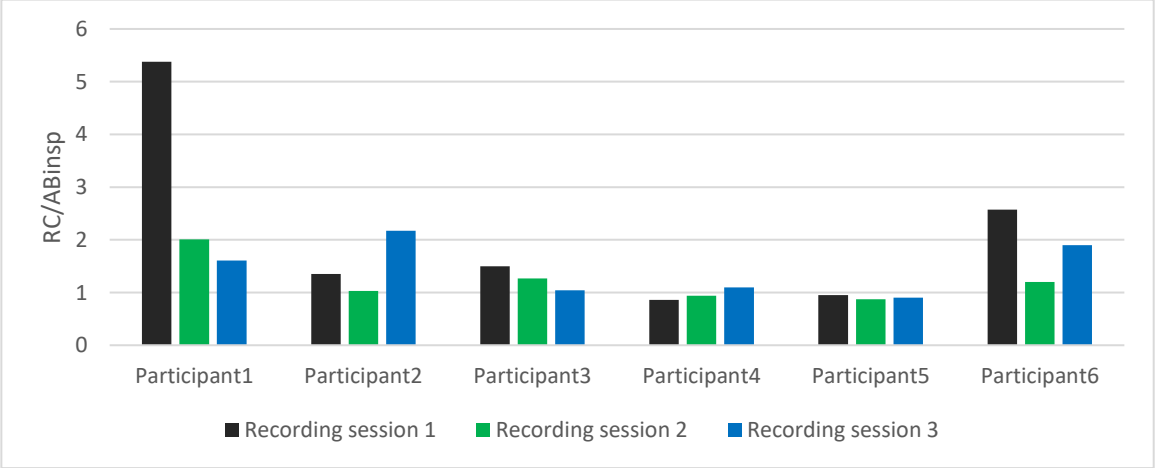


(c)

Figure 7-7: Illustartion of the changes in the absolute measurements of the examined breathing pattern components for each participant across the three recording sessions. (a) RR, (b) Ti/Te and (c) $RC_{ampinsp}/AB_{ampinsp}$

7.3.6 Responsiveness of %CoV of the examined breathing components following breathing retraining

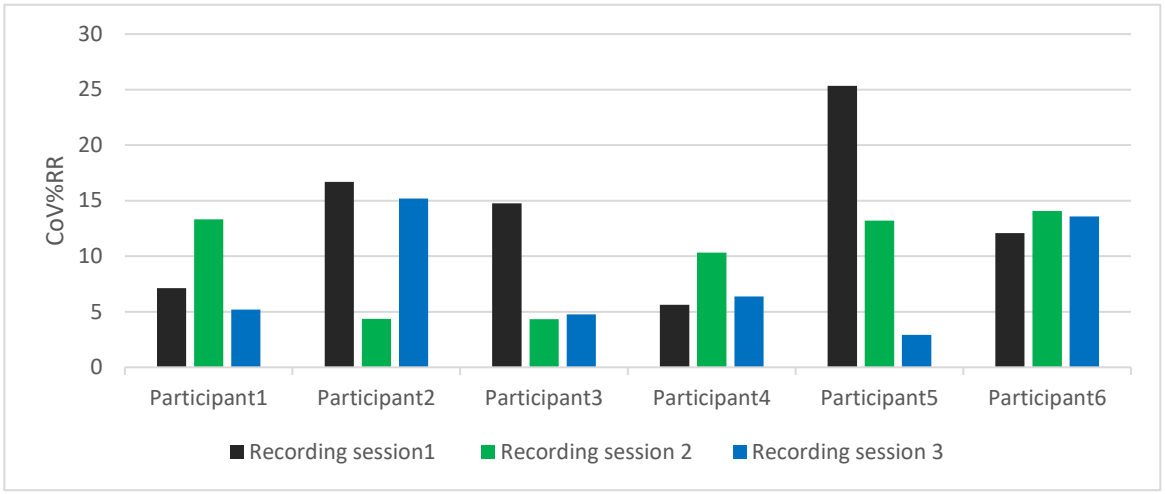
The Table 7-9 provides a summary of the estimated %CoV of the examined breathing components for each participant during the three recording sessions. A decrease in the $\%CoV_{RR}$ was observed in 4 participants between baseline and the 3rd recording session (see Figure 7-8). The decrease in the $\%CoV_{RR}$ among those participants varied from 1.24% to 22.42% and 3 out of them had well controlled and partially controlled asthma with no DB at the end of the study. Of the 4 participants, who had a decreased $\%CoV_{RR}$ after breathing retraining, two participants had a decrease in the $\%CoV_{RR}$ between baseline and the 2nd recording session (participant 2 and 5, see Figure 7-8a).

The $\%CoV_{Ti/Te}$ results showed a similar pattern of changes within participants after breathing retraining (see Figure 7-8b). Five out of 6 participants had a decreased $\%CoV_{Ti/Te}$ after breathing retraining. From those, 3 participants also had a parallel decrease in the $\%CoV_{RR}$ after breathing retraining and those were the participants with well-controlled and partially controlled asthma with no presence of DB. Decrease in $\%CoV_{Ti/Te}$ between baseline and the 3rd recording session varied from 11.71% to 17.49%. The participant who had increased $\%CoV_{Ti/Te}$ after breathing retraining was one of them with deteriorating medical condition across all recording sessions with uncontrolled asthma and presence of DB throughout the study (participant 2, see Figure 7-8b)

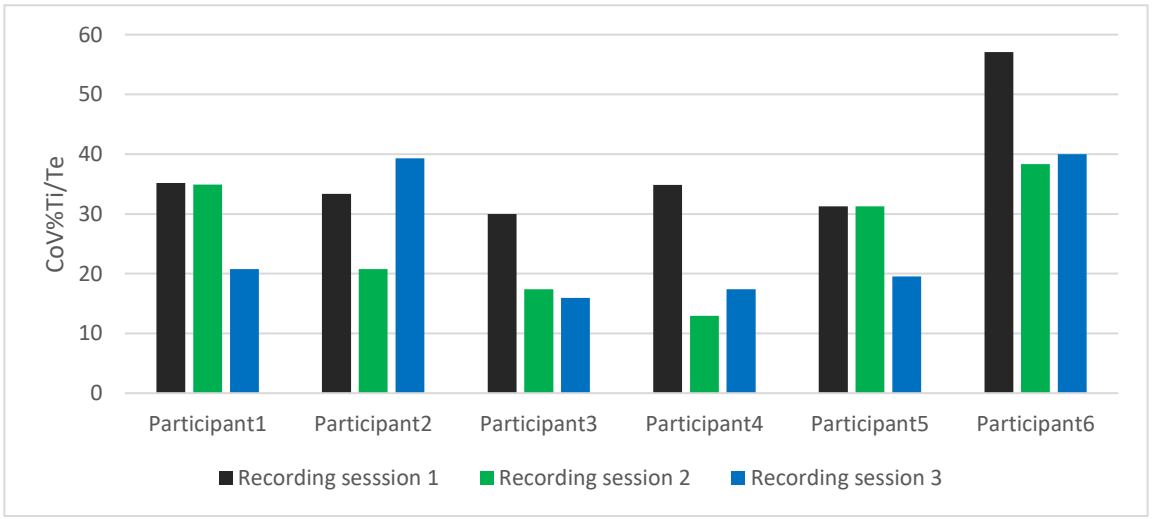
The results about the $\%CoV_{RCampinsp/ABampinsp}$ were less consistent. Three participants had a decrease in the $\%CoV_{RCampinsp/ABampinsp}$ from baseline to the 3rd recording session (see Figure 7-8c). Those were clinically stable and had $\%CoV_{RCampinsp/ABampinsp}$ >20 at baseline. Two of these participants had a parallel decrease in both $\%CoV_{RR}$ and $\%CoV_{Ti/Te}$ after breathing retraining. Participant 3, who remained clinically stable throughout this responsiveness study, had a relatively stable $\%CoVRC_{ampinsp}/AB_{ampinsp}$ across all the three recording sessions (see Figure 7-8c). It is worth to note that this participant had a normal $\%CoV_{RCampinsp/ABampinsp}$ at baseline, as based on the indicative cut-off point of this parameter suggested by the data from the correlational study.

Table 7-9: Overview of the %CoV of the examined breathing components for each participant during the three recording sessions

Breathing component	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6
$\%CoV_{RR}$						
Session1	7.14	16.68	14.77	5.63	25.35	12.08
Session2	13.32	4.35	4.33	10.34	13.21	14.08
Session3	5.20	15.21	4.75	6.37	2.93	13.58
$\%CoV_{Ti/Te}$						
Session1	35.16	33.33	30.00	34.86	31.25	57.08
Session2	34.93	20.78	17.37	12.97	31.26	38.31
Session3	20.77	39.31	15.92	17.37	19.54	40.00
$\%CoV_{RCampinsp/ABampinsp}$						
Session1	21.37	8.07	9.6	24.18	24.74	18.13
Session2	15.97	13.2	9.53	23.83	23.79	12.50
Session3	6.96	49.63	11.06	13.18	19.56	32.10



(a)



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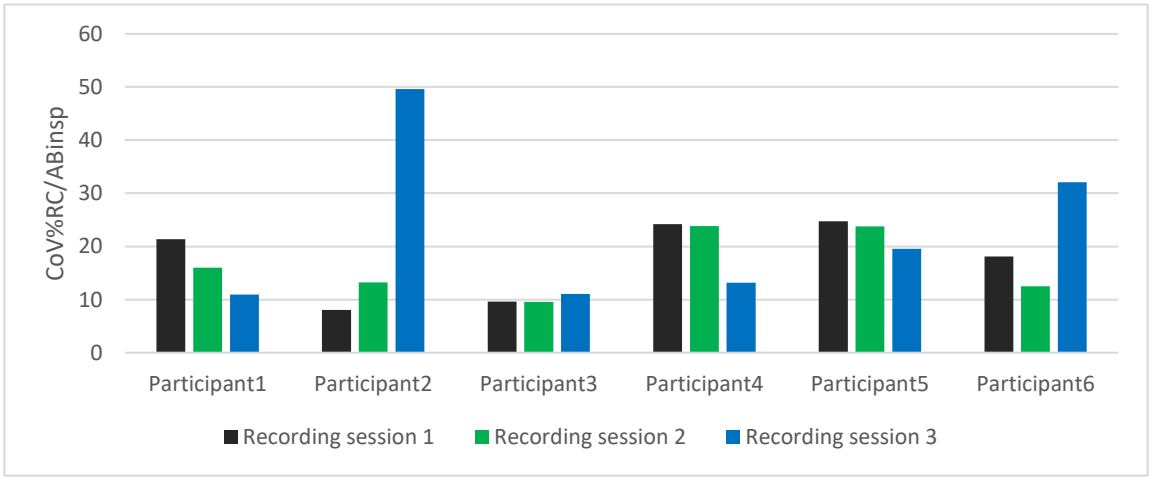

(c)

Figure 7-8: Illustration of the changes in within-individual variability of the examined breathing pattern components for each participant across the three recording sessions. (a) $\%CoV_{RR}$, (b) $\%CoV_{Ti/Te}$ and (c) $\%CoV_{RCampinsp/ABampinsp}$

7.4 Discussion of the responsiveness study

7.4.1 Effectiveness of breathing retraining as applied in this study

A body of research into breathing retraining for asthma has showed that it is an effective adjuvant treatment (Freitas et al. 2013; Courtney 2017; Bruton et al. 2018). Breathing retraining can improve asthma symptoms (O' Connor et al. 2012; Freitas et al. 2013, Courtney 2017) and asthma-related quality of life (Freitas et al. 2013; Bruton et al. 2018), even though it is not a disease-modifying treatment. The small sample size recruited in this responsiveness study makes it impossible to draw any firm conclusion about the effectiveness of the breathing retraining programme on these asthma-related outcomes.

On the other hand, there was a trend towards seeing improvements in asthma control. Although half of the participants had well controlled (n=2) or partially controlled asthma (n=1) at the end of this responsiveness study, an overall decrease in the ACQ scores was observed in all participants of this study after breathing retraining. This can show that the participants had less frequency of asthma symptoms following the applied physiotherapy breathing retraining programme. This along with an overall increase in the mini-AQLQ scores, which was found for all participants after breathing retraining, indicate the possible effectiveness of the breathing retraining programme followed in the study presented here. The applied physiotherapy breathing retraining programme was in accordance with a previously published effective breathing retraining protocol by Thomas and Bruton (2014). In addition, the participants in this small responsiveness study showed a decrease in their SABA use after breathing retraining, which is consistent with previous findings by O' Connor et al. (2012) and Freitas et al. (2013).

Traditionally, breathing retraining techniques were believed to be effective by reducing the hyperventilation that is frequently observed in patients with asthma (see section 2.3.1). However, evidence that this occurs is lacking. Those breathing retraining for asthma studies which do report levels of CO_2 before and after breathing retraining report variable results, causing doubts about the physiological mechanism underlying this intervention (Holloway et al. 2007; Thomas et al. 2009; O' Connor et al. 2012). No significant changes in CO_2 or in other physiological outcomes, such as the lung function and biomarkers, have been identified (Bruton et al 2018). Thus, this intervention is now considered to be a more behavioural technique, which may teach patients to deal better with the effects of asthma on their medical condition, by improving asthma-related quality of life (Bruton et al. 2018). It had been hoped that this responsiveness study would cast some light onto the mechanisms behind breathing retraining, to confirm whether a range of breathing pattern components changed significantly. The limited recruitment has meant that this

has not been possible, but the data from this study provide some preliminary proof-of-principle data to support future larger trials.

7.4.2 Changes in quantifiable breathing pattern components after breathing retraining programme

The findings of this responsiveness study suggest a trend towards changes in some of the examined quantifiable breathing pattern components. It appears that a pattern of positive response to breathing retraining was more likely to be observed for the RR and the %CoV of the examined breathing pattern components. There is little published evidence recording quantifiable breathing pattern components after breathing retraining. This makes comparisons with previous literature somewhat challenging. Although breathing retraining was specifically designed to modify breathing pattern components, such as the RR, the AB motion and the regularity of them, most of the published studies have not directly measured them. These published studies have relied upon using subjective questionnaires, such as the NQ (Thomas et al. 2003; Hagman et al. 2011; Freitas et al. 2013; Thomas and Bruton 2014; Jones et al. 2015; Bruton et al. 2018).

Improvements in the NQ scores have been assumed to indicate potential changes in breathing patterns. Such changes have been documented after breathing retraining in asthma (Thomas et al. 2003; Hagman et al. 2011; Bruton et al. 2018). The data from this responsiveness study also showed a pattern of decrease in the NQ scores in all participants, with half of them reducing theirs score to less than 10, suggesting no presence of DB at the end of the study. However, although initially designed to identify physiological hyperventilation, the authors of the NQ have recently suggested that it has a more behavioural perspective, showing a subjective aspect of breathing pattern changes (Dixhoorn and Folgering 2015).

Whatever the NQ is actually measuring, it is not able to provide direct information about breathing pattern components, as has been achieved in this responsiveness study. Very few researchers have also attempted to do this. Courtney et al. (2011) used the manual technique known as the MARM, to quantify the extent of thoracic dominance during resting breathing after a breathing and relaxation protocol in 62 patients with medically unexplained dyspnoea. The authors reported a positive response, suggesting there was less thoracic dominant breathing, but half of the participants in our responsiveness study showed a similar response. However, the populations being studied and the breathing retraining protocols were different and the measurement tool used by Courtney et al. (2011) relies on perceived displacement of the THA movements. It records a physiotherapist's impression of the directions and a relative dominance

of the upper RC motion to the AB motion, by giving a score of balance between these two compartments.

To date, only one piece of similar published research, using a validated recording device for breathing pattern measurements, has been identified. This is a case study by Tehrany et al. (2018) conducted to look at the responsiveness of a number of quantifiable breathing pattern components after breathing retraining during different breathing conditions (resting breathing and speech breathing). The authors used the RIP to quantify similar quantifiable breathing pattern components to those studied in this responsiveness study, following a similar breathing retraining protocol as used here. Unfortunately, due to some equipment failure, there was corruption of the authors' data for all baseline measurements during resting breathing. There were therefore no data to make pre and post comparisons, which could be also compared with this responsiveness study. However, the authors described a normal RR (14.68 bpm), but remaining thoracic breathing (82.23% of RC contribution to tidal breathing) after two breathing retraining sessions. This is in line with the findings of this responsiveness study regarding the RR changes after breathing retraining, but they are contradictory to the findings about the responsiveness of RC_{amp}/AB_{amp}, which was variable in this small sample.

In the responsiveness study, the RR was more likely to reduce in those who had a raised RR at baseline measurement and had stable medical condition across the three recording sessions. This was also observed in the %CoV of all examined breathing components, suggesting that breathing retraining may be more effective in those with an altered breathing pattern prior to implementation of this intervention. In the asthma literature, there has been no published work focused on the optimal selection of patients, who might benefit more from a breathing retraining programme, mainly because studies have not been large enough to permit useful subgroup analyses. A systematic review by O' Connor et al. (2012) suggested that breathing exercise protocols, which targeted asthma patients with hyperventilation, might be more effective than those implemented in a general asthma population. However, the conclusion of this systematic review should be interpreted with caution, as many of the included RCTs did not confirm the presence of hyperventilation with measurements of CO_2. This responsiveness study is also too small to make firm conclusions about the characteristics of patients who are most likely to show benefits from breathing retraining. However, this responsiveness study has been the first to provide preliminary objective data about the responsiveness of within-individual breathing pattern variability following a physiotherapy breathing retraining programme.

Due to a lack of evidence, no comparisons of the results for breathing pattern variability after breathing retraining can be made with previous research. In this study, within-individual

variability of the timing components of breathing pattern tended to decrease, whereas the within individual variability of proportionality of RC_{amp} to AB_{amp} had less consistent response. It had been expected that the participants would adopt a breathing pattern with more AB displacement than RC displacement in a regular pattern of motion over time, as this is something that is taught during breathing retraining. However, another elements of breathing retraining is to teach a stable breathing, characterised by slow rate of breathing with both longer inspiratory and expiratory phases, and to induce respiratory pauses. Some of the participants appear to have achieved this goal as a pattern of reduced both RR and %CoV of timing parameters was observed in this responsiveness study.

7.4.3 Breathing pattern components showing an inconsistent response to the breathing retraining programme

Although this small sample showed trends towards positive responses of the RR and the breathing pattern variability to breathing retraining, this was not observed in all participants and across all the recording sessions. So it is impossible to drawn firm conclusions from this study. Nevertheless, some of the inconsistency could have been due to alterations in participants' health status between the recording sessions. For instance, participants whose asthma worsened during the study, had inconsistent breathing pattern response with those being clinically stable between all the recording sessions. Participants, who remained clinically stable, with well controlled or partially controlled asthma at the end of this responsiveness study, were also those who showed a decreased RR and variability of the examined breathing components after the breathing retraining programme. However, more research is required to involve studies which will be large enough to be able to factor in any underlying changes in participants' health during the length of any study involving repeated measures.

Contradictory responses were observed for absolute measurements of breathing pattern components, such as the proportionate movements of the THA (RC_{amp}/AB_{amp} during both respiratory phases) and the response of the proportions of inspiration to expiration phases (Ti/Te), to breathing retraining. Although a decrease in the RC_{amp} to the AB_{amp} was seen in the majority of the participants, none of these participants were found to have predominantly abdominal breathing after breathing retraining. Since breathing retraining encourages the use of abdominal breathing, this finding was not expected. A reason for this finding could be due to any posture effect, which was also found as a confounding factor for possible influence of its relationship with asthma control and presence of DB in the correlational study of this thesis. Although the seated posture is not likely to affect measures of within-individual variability of the THA movements, it could affect the absolute measurements of freedom of movement of the AB.

It may therefore be preferable to examine responsiveness of absolute measurements of breathing mechanics in other postures, which facilitate the AB displacement, such as semi-supine posture, as previously supported in the correlational study.

Additionally, timing changes in the absolute measurements of Ti/Te were inconsistent. It was expected that participants would adopt a longer Te than Ti. Although reduced rate of breathing was observed, it is quite likely that both timing phases altered irrespective of which from the two phases changed more. Looking at the proportion of the Ti/Te, this could have been missed. However, although longer Te than Ti was not see in all participants at the end of this responsiveness study, the within-individual variability of the Ti/Te did reduce almost in all participants apart from one who had acute allergy and chest infection on the day of breathing pattern recordings. Taken together with other findings, it seems that measuring within-individual variability of breathing pattern components, rather than taking absolute measurements derived by single-time measurements of them could be a better variable to see any response to breathing retraining.

Some of the inconsistency in findings may relate to the amount of practice that individuals gave for breathing retraining. Although the programme followed the protocol used in a previous successful RCT in terms of face-to-face breathing retraining sessions (Bruton et al. 2018), there was no way to be ensured about how much time participants practiced at home. This could be a factor for inconsistent changes among examined breathing pattern components in this responsiveness study. In this study, the participants self-reported the time spent practicing breathing exercises at home as advised by the specialist physiotherapist. They reported practising from 2 to 4 times a day. The participants who practiced 4 times a day were those with a reduced RR and %CoV of the examined breathing patterns at the end of the study compared to those who practiced once a day. However, firm conclusions about this potential relationship cannot be drawn from this small responsiveness study.

Moreover, the patients' self-reports should always be interpreted with caution because participants may inflate reality to please the researcher. Mortel (2008) has explained the socially desirable response theory, which was described as the tendency of individuals to present a favourable image of themselves in experimental studies. Any future studies that might aim to examine a dose-response relationship for breathing retraining, would need to find a better and objective measure of adherence than participants self-reports.

To date, there is no recommended amount of time for practicing breathing exercises or for the total duration of physiotherapy breathing retraining programme. Bruton et al. (2018) reported that the time spent for practising breathing exercises at home was variable among their

participants and was not significantly related to improvements in asthma quality of life. Although this suggests that a dose-response between breathing retraining and subjective asthma-related outcomes was not evident in their study, intuitively this might not be applicable for some association between time spent practicing and having success at adopting a different breathing style as reflected by direct changes in quantifiable breathing pattern components. For example, Grammatopoulou et al. (2011) conducted a RCT involving a breathing retraining programme and they reported that participants in the intervention group did not develop behavioural adaptation of their breathing until after 6 months. However, this was based on participants' perception of their own breathing, rather than on direct objective physiological elements of breathing.

7.5 The limitations of the responsiveness study

One of the main limitations preventing any firm conclusions is the small sample recruited for this responsiveness study. Although this work can be used to provide preliminary data of breathing pattern responsiveness, a much larger sample is required to enable any generalisations of the results. A larger sample would have been also enabled to determine significance of any observed change in the examined breathing pattern components and their association with changes in asthma control and presence of DB over time. This small study used an uncontrolled observational repeated measures study design to look at the response of specific quantifiable breathing pattern to breathing retraining. Although the effectiveness of this intervention is well-recognised on other patient-related outcomes, such as asthma-related quality of life, a RCTs with repeated measures would allow to ensure any actual significant treatment effect of breathing retraining on quantifiable breathing pattern components, beyond some observations of pattern of changes as identified in this responsiveness study.

In addition, a lack of participant blinding regarding breathing pattern measurements could be considered as another limitation of this study. This could have contributed to any observed response to the intervention in such a small study. The participants' awareness of being recorded can have a potential effect on breathing pattern measurements. This may have an impact on breathing pattern measurements after receiving an intervention for modifying breathing. The patients could have become more aware of their breathing after undertaking breathing retraining sessions. In this responsiveness study, breathing pattern components were measured using the SLP. Although it is possible to dissimulate the precise start and end of time of breathing pattern recordings, it is not possible to blind participants to the fact that they are being recorded. Distraction techniques may be useful to prevent participants focusing on their breathing during recordings. This may enable the measurement of a more natural behaviour of participants'

breathing patterns, especially in those who receive modification techniques, minimising any breathing pattern manipulation by the patients during recording process.

As discussed earlier, although sitting posture is one of the routine postures for patients to be examined in clinical practice, sitting may not be the ideal posture to record the THA movements in studies looking at the responsiveness of absolute measurements of compartmental displacements of the THA. Posture effect on breathing mechanics is likely to restrict the spontaneous AB displacement which is a key element that patients are being taught in breathing retraining programmes.

7.6 Summary of the responsiveness study

No firm conclusions are possible from this small study. Although some changes in the examined breathing pattern components were seen after breathing retraining, these were generally inconsistent. The components of breathing pattern showing the most consistent response were the RR and the within-individual variability of the examined breathing components. Firm conclusions cannot be drawn about the association of changes in breathing pattern components and asthma control or presence of DB over time. However, in this responsiveness study a maintenance of the association between asthma control, DB and the breathing pattern variability could be observed in half of the sample of this responsiveness study after breathing retraining. Beyond the above, this responsiveness study has confirmed the feasibility and acceptability of breathing pattern data collection in a clinical setting. The study has therefore provided the groundwork necessary to prepare for future clinical trials looking at the use of quantifiable breathing pattern components to monitor treatment effects after breathing retraining.

Chapter 8 An overall discussion of the key findings of this research

In this chapter, a summary and a combined discussion of the key findings of the research presented in this thesis are provided. To be reminded, the original aim of this research was to explore whether quantifiable breathing pattern components, such as timing parameters and THA movements, could be used as a supplemental physiological marker in asthma management. This was successfully examined through three experimental studies: 1) an initial equipment validation study to establish the validity and the responsiveness of Structured Light Plethysmography (SLP) compared to the Respiratory Inductive Plethysmography (RIP) prior to a selection of suitable form of technology for breathing pattern measurements in the subsequent studies, 2) a correlational study to establish whether these breathing pattern components could primary predict asthma control and secondary be associated with other asthma-related outcomes and 3) a responsiveness study to establish if breathing pattern components alter after a clinical physiotherapy breathing retraining programme, designed to change breathing patterns.

8.1 Using the Structure Light Plethysmography as a valid and responsive tool for breathing pattern measurements

There is a variety of different monitoring tools, which are used to evaluate breathing patterns. In clinical practice, breathing pattern disorders are detected by clinicians' observations or subjective questionnaires, such as the NQ. Although simple observations can be easily performed, they can lack accuracy (Tulaimat et al. 2016). Questionnaires, such as the NQ, are also under criticism due to their reliance on patients' perception about their breathing (Van Dixhoorn and Folgering 2015). This is likely to provide a subjective aspect of breathing problems without involving direct measurements of its physiological elements. Due to the difficulties with quantifying breathing pattern components, they have been infrequently recorded in clinical practice and are therefore not used routinely to evaluate respiratory diseases, such as asthma.

Technological advances have now allowed the development of monitoring technologies, which objectively and accurately quantify a range of breathing pattern components over time (Clarenbach et al. 2005; Fiamma et al. 2007; Layton et al. 2013; Viera et al. 2015). However, current technologies, such as the RIP and the OEP, are used mainly for research rather than in clinical practice. The main reasons for this are the equipment size, the complexity of equipment use, and the data analysis of recorded breathing patterns. A relatively new form of technology,

known as the Structured Light Plethysmography (SLP), was identified when current validated technologies for breathing pattern measurements were reviewed in this thesis. Although deemed to be a promising technology, there is a limited body of evidence examining its validity and responsiveness for breathing pattern masurements under different breathing conditions compared to other non-invasive recording methods.

This research achieved to contribute to the knowledge relating to the SLP's validity. This technology generated valid data when measuring breathing timing parameters and the proportion of regional displacements of the THA (RC_{amp}/AB_{amp}) during both resting and fast breathing, as compared to the RIP. The same validation study also provided evidence of the ability of the SLP to detect changes in timing parameters and the RC_{amp}/AB_{amp} during both respiratory phases between resting breathing and immediately after exercise. Those changes were in agreement with the RIP, and thus its suitability for use in the correlational study and responsiveness study of this thesis was determined. Using the SLP in this research have enabled to identify both theoretical advantages and disadvantages of this technology in comparison with other current recording methods. This may influence its future utility in either research or clinical practice.

Using the SLP for breathing pattern measurements, has the advantage to provide objective valid direct assessments of a range of breathing pattern components over time compared to other current subjective methods, such as the clinician's observations or questionnaires. These are based either on health professionals' expertise or on patients' perception, limiting an objective and direct quantification of a range of quantifiable breathing pattern components over time. In comparison with other technologies, such as the OEP, one of the advantages of SLP is its ease of use and its portability without requiring spacious laboratories within the clinical settings. Furthermore, the SLP can provide instant analysis and quantification of breathing pattern data via its automatic software, compared to other existing recording methods, such as the RIP. The latter one requires signal-processing techniques for breathing pattern analysis. Although the validity of the SLP's analytical software was beyond the scope of this research, having an instant automatic analysis of the recorded data could facilitate the instant breathing pattern analysis in different clinical environments, such as from primary care to community settings.

The feasibility of using the SLP in different clinical settings has been previously reported by Elshafie et al. (2016) and Motamedi-Fakhr et al. (2017b), suggesting that this device can be a clinical tool for evaluating quantifiable components of breathing patterns in clinical practice. These authors did not report any negative factors about the SLP, but from the researcher's experience during this research, there are a few issues with this technology. The SLP's recording

approach relies on optical-based methods, which can sometimes be interfered with natural or artificial light. External light sources can affect the projection of the grid pattern onto the individuals' THA, resulting in the inability of the two cameras to detect distortion of the grid pattern's intersection points. This, in turn, can result in introducing artifacts within the SLP signal during data acquisition. To prevent this potential issue, breathing pattern recordings for all three studies presented in this thesis occurred in laboratories with low level of lighting. However, if the SLP is to be used in future within environments with brighter lighting, this issue is required to be overcome.

Another issue is that the SLP requires individuals to stay still and quite for acquiring good quality of data for maximum 5 minutes of recording. The SLP is sensitive to body movements, which can be another factor for introducing artifacts within its signal. Staying still and quiet for maximum 5 minutes of breathing pattern recording can be feasible, gaining participants' acceptance as demonstrated in the three studies of this research. Nevertheless, breathing pattern recordings obtained by the SLP may not be feasible during exercise, such as on an ergometer or during ambulatory activities. Thus, the SLP is likely to be better suitable for recording breathing at rest and for a specific period of time. However, the 5 minutes of resting breathing pattern measurements performed in this research was deemed a sufficient time to obtain measurements of both absolute measurements and within-individual variability of the examined breathing pattern components.

To date, the SLP validity has not yet been tested in other groups or under different postures from those used in the validation study (healthy adults with normal BMI in sitting position) and the few published studies (healthy adults, patients with COPD, asthma, or lung recession in sitting position) (Elshafie et al. 2016; Motamedi-Fakhr et al. 2017b). Using different technologies, postures and the BMI have been previously reported to have an impact on breathing pattern components, such as volumetric indices and the THA movements (Parreira et al. 2010; Kameko and Horie 2012). Although the same technology and posture was used across the three studies of this research, individuals with variable BMI and different body types were recruited across the 3 studies of this research.

The inclusion of obese participants may have affected some of the findings of the correlational study and the responsiveness study. Since the SLP's performance has not rigorously evaluated in this group of patients, it is acknowledged that some discrepancies between the ability of the THA movements and the ability of timing components to evaluate asthma control or presence of DB may have been reasonably found. In the responsiveness study, the variable changes observed more in parameters associated with the THA movements could have been also attributed to the

use of the SLP in a sample mainly comprised of obese asthma patients. Thus, more research into the SLP validity is required to assess its performance in patients with both high and low BMI. However, to date, there is no an optimal method for measuring the THA movements in obese individuals, as both the RIP and the OEP have been reported to underestimate volumetric indices and regional displacements of the THA in these individuals (Boudarham et al. 2013; Hollier et al. 2014).

On the other hand, two major advantages of the SLP as a new form of recording method are its fully-contactless recording approach requiring minimal individuals' cooperation, compared to other methods, such as the lung function tests (Levai et al. 2012). Lung function tests lean on the individuals' ability to perform a maximal expiratory manoeuvre. Also lung function tests are mainly performed in specialist clinical centres where experienced personnel should evaluate and interpret Spirometry results (Miller et al. 2005). The SLP requires minimal individuals' cooperation gaining the patients' acceptance according to this research. This together with its ease in use and the instant analysis of breathing pattern data has the potential to facilitate the routinely assessment of breathing pattern components not only is specialist clinical centres, but also in different clinical settings, such as primary care or community settings. Moreover, the SLP has been reported not to induce instrumental changes in breathing pattern measurements and has been speculated to minimise individuals' awareness of breathing measurements (Nierat et al. 2017). Thus, this makes the SLP a suitable method for recording the natural behaviour of breathing whose a range of objective physiological elements can be quantified and used in relation to asthma control.

8.2 The use of breathing patterns as a physiological marker in asthma management

The overall aim of this research was to explore the use of breathing pattern components as a physiological marker in asthma management. This was achieved by conducting both the correlational study and the responsiveness study. New knowledge has been generated through this research, which suggests that, timing components and THA movements have a role as a physiological marker in asthma management. Specifically, the within-individual variability of timing components, such as RR and Ti/Te, and the proportionality of regional displacements of THA (RC_{amp}/AB_{amp} during both respiratory phases) were found to predict asthma control and differentiate between people with well-controlled and uncontrolled asthma. The within-individual variability of the examined breathing pattern components was a better parameter for reflecting the behaviour of breathing in relation to asthma control than the use of absolute measurements

of them when measured on one occasion. Considering these findings of the research, the importance of a stable breathing as a reflector of asthma control was identified in this research (see section 6.4.1.1). The variability of these breathing pattern components were also found to present a more consistent pattern of changes in the responsiveness study, but no firm conclusions could be drawn due to the limitations identified in this study (see section 7.5).

The absolute measurements of the examined breathing pattern components were not found to be significantly associated with asthma control or any other asthma-related outcomes as examined in the correlational study. This could be mainly attributed to the presence of confounding factors having a potential impact on these measurements as identified in a cross-sectional correlational study. The author suggested that some of the key confounders were a postural effect, the emotional arousal, an extreme BMI and a potential effect of the rescue medication use on breathing pattern measurements. Previous published research has reported that some of these factors can alter absolute measurements of breathing patterns (Masaoka and Homma 1999; Homma and Masaoka 2008; Parreira et al. 2010).

Although the breath frequency was found to be a significant predictor of asthma control and of all the other asthma-related outcomes examined in the correlational study, the above confounding factors may have been also responsible for their non-linear relationship (see section 6.4.1). However, it is less clear whether these confounding factors have an impact on the variability of breathing pattern components. In both correlational and responsiveness studies, these confounding factors were not found to cause contradictory findings for measurements of breathing pattern variability. A linear relationship was found between the within-individual variability of the examined breathing pattern components and the asthma control or the presence of DB. Thus, breathing pattern variability is likely to be a better measurement to be obtained in single time assessments in asthma management. This comes to further support the evidence indicating that measuring the natural behaviour of the respiratory system over time is more likely to reflect better its adaptability required during symptomatic periods of respiratory diseases (Frey et al. 2011).

The finding that within-individual variability of breathing pattern components is a better reflector of asthma control than their absolute measurements is in agreement with previously published evidence regarding other physiological markers, such as the lung function and biomarkers (Matsunaga et al. 2014; Manoharan et al. 2015). Single point measures of lung function and biomarkers, have been reported to be less useful than fluctuations of them between different recording sessions at predicting asthma control or future asthma exacerbations (Bora et al. 2011; LeBlanc et al. 2013; Matsunaga et al. 2014; Manoharan et al. 2015; Grzelewska-Rzymowska et al.

2015). However, to date, physiological markers, such as the lung function and biomarkers, have not been found to be able to guide adjunctive asthma treatments, such as breathing retraining.

This research additionally examined the responsiveness of the examined breathing pattern components after a physiotherapy face-to-face breathing retraining programme to further explore their use as a physiological marker in asthma management. This research suggests that some of the breathing pattern components do show some responsiveness to change after breathing retraining. However, any response of the examined breathing pattern components in response to breathing retraining cannot be deemed to be the result of this intervention. This was due to the use of a small experimental uncontrolled study. The clinical effectiveness of the applied intervention was determined by a consistent pattern of changes in asthma-related quality of life scores. This was in agreement with a previously published RCT reporting improvement in asthma quality of life scores after applying a similar breathing retraining protocol (Bruton et al. 2018). The components of breathing patterns, showing a consistent response to breathing retraining, are those that were also found to be significant predictors of asthma control, and be a surrogate marker of DB and poor quality of life in the correlational study.

There are additional reasons for not obtaining consistent responses among all the examined breathing pattern components in the responsiveness study, beyond the methodological limitations relating to the selected study design (discussed in more detail in section 8.3). As mentioned previously, the stability of the participants' clinical condition across the three recording sessions could be an important factor affecting the changes observed in both absolute measurements of breathing patterns and the variability measures of breathing pattern components across all the participants. Participants, who were experiencing asthma worsening due to acute allergies or chest infection, would be unlikely to show any benefits from the breathing pattern intervention. This could be masked by having a clinically unstable health condition. However, despite the fact that only one participant in particular showed deterioration in her clinical health throughout the responsiveness study, all participants reported an increase in asthma quality of life scores.

This together with previously reported weak associations between patient-reported outcome measures and other physiological markers, such as lung function after breathing retraining interventions (Bruton et al. 2018), may support the theory that there is a psychological effect associated with this intervention. This has been previously reported by Thomas et al. (2017). Asthma patients, receiving adjunctive asthma treatments, such as breathing retraining, are also educated to manage the long-term consequences of their asthma and this may change their perception about their quality of life. However, this effect may not be reflected as an

improvement in other physiological outcomes, such as quantifiable breathing pattern components.

In contrast, in the correlational study, the increased breathing pattern variability was associated with poor asthma quality of life, suggesting some interrelation between stable breathing and quality of life. However, this association was identified in a different sample from the one involved in the responsiveness study. It is not known if participants in the correlational study had previously received any breathing exercises or how well informed they were to manage their clinical condition. Beside this, the participants in the responsiveness study may have attempted to present a favourable picture of themselves, due to their awareness of the study's purpose. This was to look at changes in both patient-related outcomes and breathing patterns before and after breathing retraining.

In addition to the above, insufficient practice of breathing retraining techniques for adopting a permanent modified breathing pattern is recognised to be another potential reason for the observed inconsistent responses among some of the examined breathing components to this intervention. A dose-response relationship between breathing patterns and breathing retraining is not currently known and no firm conclusions can be drawn from the data of the responsiveness study of this research. However, adaptation of a permanent slow abdominal breathing pattern, with longer expiration phases, may require more practice over a longer period than this performed in the responsiveness study. Small changes after breathing retraining captured by the absolute measurements of breathing pattern components, such as the RC_{amp}/AB_{amp} and the Ti/Te, may be missed unless a consistent abdominal breathing with longer expiration is maintained during the whole recording session. On the other hand, a more consistent pattern of changes were observed for the variability of the examined breathing pattern components. This may be a more sensitive parameter to respond to breathing retraining, capturing the continuous behaviour of breathing over time.

A final key finding from this research is the identification of new physiological components of breathing patterns to be used as a surrogate marker for the presence of DB. These were the within-individual variability of timing parameters (RR, Ti/Te), and RC_{amp}/AB_{amp}. The identification of this association meets the emerging need for using objective clinical measurements to characterise and detect DB in asthma as previously suggested by Van Dixhoorn and Folgering (2015). Given the multidimensionality of breathing, a single criterion, such as the NQ based on patients' perception, may not be sufficient to establish the presence of DB in asthma and multicomponent assessments are required. Therefore, identifying more physiological elements in

addition to these identified from this research and previously published literature may enhance a better characterisation of DB, and its accurate detection in clinical practice.

8.3 Reliance of the research findings on observational and experimental uncontrolled studies

The identified association between the examined breathing pattern components and outcomes involved in this research is based on an observational cross-sectional study design, applying a regression analysis. For instance, this observational cross-sectional study allowed the researcher not only to identify an empirical association between the breathing pattern variability and asthma control, but also enabled the researcher to explore the ability of breathing pattern components to evaluate asthma control. This enabled the author to meet the primary aim of this research, which was to explore the use of breathing patterns as a physiological marker in asthma management. However, the selected design of the correlational study does not permit the identification of any causal relationship between these variables. This is because correlation only provides information about association between variables, not the cause of the relationship (Boyko 2013). Although within-individual variability could predict asthma control, these parameters were measured at the same single time point. Thus, it is not known whether increased within-individual variability of breathing pattern components preceded uncontrolled asthma or vice versa, despite their ability to predict uncontrolled asthma as performed on one occasion in this research.

Maintenance of the association between the within-individual variability of breathing pattern components and asthma control over time could not be ascertained from the correlational study. Although this could be looked at the responsiveness study including repeated measurements of the variables over time, firm conclusions could not unfortunately be drawn, due to the study's limitations. Therefore this should be addressed by future prospective cohort studies, which are required not only to establish a causal relationship between these variables, but also to cross validate the results of this research. In addition, observational cross-sectional studies are also likely to be prone to confounding factors compared to other observational studies, such as cohort studies (Boyko 2013). For instance, in the correlational study, absolute measurements of the examined breathing pattern components were found to be prone to confounding factors. This has been attributed to cause bias in their relationship with the examined variables of this research. An example of this is the violation of linearity between the RR and all the patient-related outcomes examined in the correlational study, despite being a significant predictor of them.

Research design was also a factor affecting the interpretation of the responsiveness study. It involved an interventional single-arm (uncontrolled) study with repeated measures to look at

breathing pattern responsiveness after breathing retraining. As mentioned previously, this was a small study, which did not allow the testing of any hypotheses and the significance of potential associations between changes of the examined breathing patterns and patient-related outcomes. However, it enabled the observation of some consistent pattern of changes in the examined breathing pattern components after three physiotherapy breathing retraining sessions (see section 7.4). A randomised controlled trial design would have been the ideal study design to determine the actual impact of breathing retraining on breathing pattern components. This type of study would allow the inclusion of a demographically matched control group and this would make it easier to ascertain if any differences in the examined breathing pattern components were specifically due to the intervention. However, the value of the responsiveness study is that it has provided proof-of-principle data necessary to prepare for future clinical trials and the feasibility as well as the acceptability of breathing pattern data collection using a new form of technology, like the SLP, in a clinical setting.

Chapter 9 Applicability of research findings and future research direction

The research presented in this thesis aimed to explore the use of breathing patterns as a physiological marker in asthma management. An association between breathing pattern variability (timing parameters and THA movements) and asthma control was identified together with its ability to evaluate disease control. The evaluation of frequency of asthma symptoms using patients' subjective assessment is an integral part of the monitoring process of disease control (GINA 2018). Although regularity of timing parameters and the proportionality of compartmental movements of the THA can evaluate asthma control, the intention is not to replace patients' subjective assessment with these parameters in future clinical practice. Instead, measuring the variability of these breathing components could be used as an additional objective supplemental physiological marker to enhance the multicomponent monitoring process of asthma control in clinical settings. Incorporating measurements of the within-individual variability of the examined breathing pattern components of this research into subjective questionnaires, such as the ACQ, the ACT may also improve their diagnostic performance in the future. At present only the ACQ includes items regarding lung function, to provide a more objective multicomponent assessment of asthma control. However, this requires future developmental and validation work for these questionnaires.

This research should have an impact on all health professionals involved in the respiratory care, but will be of particular interest to respiratory physiotherapists who modify breathing patterns in their clinical practice. Using breathing pattern variability may enable physiotherapists' better clinical assessment of asthma patients' medical condition. Although this research was conducted in adult patients with asthma, future research in other populations such as children, could be done to observe consistency of the findings of this research in other asthma population. This research used an optical based monitoring method for breathing pattern measurements (SLP). The SLP has the potential to be a clinically useful device due its portability, ease of use and instant breathing pattern data analysis. So objective valid breathing pattern measurements may be applied in routine clinical practice instead of using subjective questionnaires. In this research, increased breathing pattern variability was secondary found to be a surrogate marker of DB as measured by the NQ. Therefore, it could become a useful method for providing objective evidence of detecting and characterising DB in conjunction with the use of the NQ in clinical practice.

Although this research achieved to establish the association between specific quantifiable breathing pattern components and asthma control, establishing the nature of their precise relationship requires future research involving prospective cohort studies. This is required to look for any causal relationship between these variables and cross-validate the results of this research. This could be achieved by measuring the breathing pattern variability and then asthma control longitudinally, over a longer period in time. A demographically and asthma phenotypically matched control group could be included in the cohort study to enable appropriate comparisons. The same prospective cohort study design can observe breathing patterns in the time leading up to asthma exacerbation. Asthma exacerbation is a detrimental factor for patients' mortality, frequent patients' hospitalisations, and distortion of their quality of life leading to uncontrolled asthma (GINA 2018). Also a future research work could involve the examination of a potential association between breathing patterns and other physiological markers, which were not included in this study, such as some of the most commonly used biomarkers in clinical practice and direct measurements of CO_2.

Future work is additionally required to confirm the responsiveness of breathing patterns to breathing retraining. This would require a RCT to record breathing pattern components before, during and after breathing retraining. In this RCT, a dose-response relationship between breathing retraining practicing and the changes in breathing pattern components could be determined. In addition to examining the impact of breathing retraining on breathing patterns, any biomechanical mechanism underlying breathing retraining needs to be determined, together with discovering the optimal selection of asthma patients, who could benefit from this effective adjunctive asthma therapy.

Chapter 10 Conclusion of this research

The original aim of this programme of research was to explore the use of breathing patterns as a physiological marker in asthma management. To address this aim, a validation study of a relatively new form of technology, known as the Structured Light Plethysmography (SLP) for breathing pattern measurements was conducted prior to implementing an observational and an experimental study involving asthma patients. Through the latter studies, associations between specific quantifiable breathing pattern components and asthma control (plus other asthma related outcomes) were examined along with their ability to respond to adjunctive asthma therapy, such as a physiotherapy face-to-face breathing retraining programme.

This research suggests that the SLP is a valid and responsive form of technology for measuring timing parameters (RR, Ti, Te, Ttot Ti/Te) and the proportionality of ribcage displacement to abdominal displacement during resting and fast breathing when compared to a current reference standard method known as the Respiratory Inductive Plethysmography (RIP). The within-individual variability among and between individuals was not a factor for violating the SLP's measuring performance. The SLP's responsiveness was also able to be concluded from this validation study, as it demonstrated the ability of the SLP to detect changes in these breathing pattern components. This recording method has the potential to be used in different clinical environments, simplifying the recording and analysis of breathing patterns and offering objective valid assessments of them. However, more research is required to determine its performance in different groups of people, with a range of demographic characteristics, and in different postures from those used in this research.

The findings of this research suggest that specific quantifiable breathing pattern components can be used as a supplemental physiological marker in asthma management. These were the within-individual variability of timing parameters (RR and Ti/Te) and the proportionality of ribcage displacement to abdominal displacement (RC_{amp}/AB_{amp}). An association between these parameters and asthma control was established in this research. Increased within-individual variability of these breathing components can significantly predict asthma control as measured at a single time point, and this physiological breathing parameter was found to be able to classify patients with well-controlled asthma and uncontrolled asthma. Absolute measurements of these breathing pattern components were found to be less useful as a physiological marker in relation to asthma control, due to being influenced by confounders. The superiority of variability measures over absolute measures was secondary found for predictions of other asthma-related outcomes

used in asthma management, such as the presence of dysfunctional breathing and the asthma-related quality of life.

This research could not draw firm conclusions about the changes in breathing pattern measurements after breathing retraining, even though a consistent pattern of changes in some of breathing pattern components was observed. Although no positive statements can be made about using the examined breathing pattern components to determine the effect of physiotherapy breathing retraining programmes, this research confirms the feasibility and acceptability of breathing pattern data collection following this intervention in a clinical setting. This provides the proof-of principle data necessary to prepare for future randomised controlled trials.

Appendix A Search strategies for narrative reviews of the literature

A.1 Use of quantifiable breathing pattern components to be associated with asthma control

Electronic databases: PubMed, ScienceDirect, EMBASE, Cochrane Database of Systematic Reviews

Times of search: November 2016- December 2016, September 2017- October 2017, April 2019- May 2019

Table A1-1: Search key terms (plus their synonyms) combined with "OR" or "AND"

"Breathing pattern"		"Asthma control"		Association	Marker
OR		OR		OR	OR
"breathing parameters" Breath* "Respiratory rate" "Timing parameters" "breathing mechanics" "Chest wall motion" "Thoracoabdominal movement" "Tidal Volume" "Dysfunctional breathing"	AND	"asthma control adequacy" "Not-well controlled asthma" "uncontrolled asthma" "poorly controlled asthm"	AND	Relation Prediction Evaluation	Outcome Indicator

Table A1-2: Eligibility criteria used to identify relevant studies

Inclusion criteria	**Exclusion criteria**
Adult patients (aged 18 or over) with a diagnosis of asthma and different severity	Studies without full access
Primary examined outcomes: timing components (RR, Ti, Te, Ttot), regional expansions of chest wall (ribcage and abdomen), volumetric indices (Vt), asthma control as measured by ACQ, ACT or any other valid method supported by GINA guidelines	Studies which were not written in English language
Systematic reviews Observational (both longitudinal or cross-sectional) studies which examined associations between above primary outcomes	Publishing year before 2000

A.2 Use of quantifiable breathing pattern components after breathing retraining

Electronic databases: PubMed, ScienceDirect, EMBASE, Cochrane Database of Systematic Reviews

Times of search: November 2016- December 2016, September 2017- October 2017, April 2019- May 2019

Table A2-1: Search key terms (plus synonyms) combined with "OR" or "AND"

"Breathing pattern"		"Asthma treatment"		Outcome
OR		OR		OR
"breathing parameters" Breath* "Respiratory rate" "Timing parameters" "breathing mechanics" "Chest wall motion" "Thoracoabdominal movement" "Tidal Volume" "Dysfunctional breathing"	AND	"Breathing exercises" "Breathing retraining" "diaphragmatic breathing" "adjunctive asthma treatment" physiotherapy	AND	Marker "Treatment effect" Responsiveness Change

Table A2-2: Eligibility criteria used to identify relevant studies

Inclusion criteria	**Exclusion criteria**
Adult patients (aged 18 or over) with a diagnosis of asthma and different severity	Studies without full access
Primary examined outcomes: quantifiable breathing pattern components such as Vt, timing parameters and regional contributions to chest wall motion Secondary examined outcomes: dysfunctional breathing measured via NQ, asthma control, asthma quality of life, lung function	Studies not written in English language
Systematic reviews Randomised Controlled Trials Experimental studies Case reports	Publishing year before 2000

A.3 Valid non-invasive monitoring methods for breathing pattern measurements

Electronic databases: PubMed, ScienceDirect, EMBASE, Cochrane Database of Systematic Reviews

Times of search: September 2016- November 2016, January 2017- February 2017, April 2019- May 2019

Table A3-1: Search key terms (plus synonyms) combined with "OR" or "AND" for identifying RIP validation studies

"Respiratory Inductive Plethysmography"		"Breathing pattern"		Validity
OR		OR		OR
"Inductive plethysmography" "non-invasive breath recording" "Non-invasive recording"	AND	"Breathing parameters" "Chest wall motion" "Thoracoabdominal movement" "Breathing mechanics" "Tidal volume"	AND	"Measurement accuracy" "Measurement agreement"

Table A3-2: Search key terms (plus synonyms) combined with "OR" or "AND" for identifying OEP validation studies

"Optoelectronic plethysmography"		"Breathing pattern"		Validity
OR		OR		OR
"optical-based recording method" "Non-invasive recording method"	AND	"Breathing parameters" "Chest wall motion" "Thoracoabdominal movement" "Breathing mechanics" "Tidal volume"	AND	"Measurement accuracy" "Measurement agreement"

Table A3-3: Search key terms (plus synonyms) combined with "OR" or "AND" for identifying SLP validation studies

"Structured Light Plethysmography"		"Breathing pattern"		Validity
OR		OR		OR
"optical-based recording method" "Non-invasive recording method"	AND	"Breathing parameters" "Chest wall motion" "Thoracoabdominal movement" "Breathing mechanics" "Tidal volume"	AND	"Measurement accuracy" "Measurement agreement"

Table A3-4: Eligibility criteria used to identify relevant validation studies for each monitoring method

Inclusion criteria	**Exclusion criteria**
Healthy adults (aged over 18 years) or adult patients with a diagnosis of a respiratory problem	Studies without full access.
Use of a comparator reference standard recording	Studies which were not written in English language
Examination of validity in different breathing conditions (at rest, during or after exercise, different breathing manoeuvres at different postures)	
Studies which examined at least one of the following examined breathing parameters: Vt, minute ventilation, RR, Ti, Te, Ti/Ttot and regional contributions of RC and AB to Vt	

Appendix B Materials used in each study included in this research

B.1 Ethical approval and materials used for participants' recruitment and data collection in the validation study

Your Ethics Submission (Ethics ID:18396) has been reviewed and approved

ERGO <ergo@soton.ac.uk>
Τετ 3/2/2016 8:47 AM
Προς: Sakkatos P. <ps4e13@soton.ac.uk>

Submission Number: 18396
Submission Name: Validation of Structured Light Plethysmography (SLP)compared to Respiratory Inductive Plethysmography (RIP)in adults
This is email is to let you know your submission was approved by the Ethics Committee.

You can begin your research unless you are still awaiting specific Health and Safety approval (e.g. for a Genetic or Biological Materials Risk Assessment)

Comments
None
Click here to view your submission

ERGO : Ethics and Research Governance Online
http://www.ergo.soton.ac.uk

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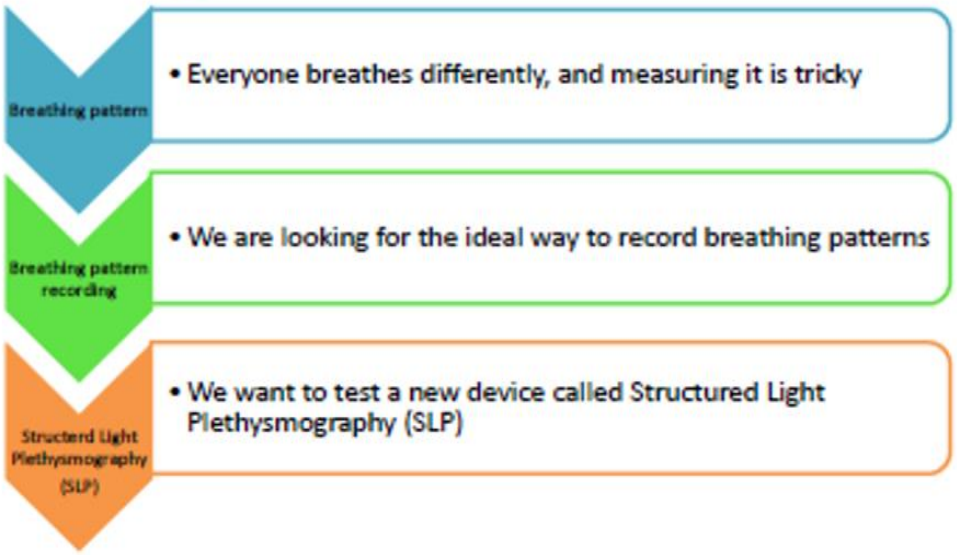
What do you know about breathing patterns?

How can a breathing pattern be recorded?

Do you want to know more about your own breathing pattern?



Are you able to help us to test the Structured Light Plethysmography?

You can take part if you are **18** or over with **no** problems that could affect your ability to pedal a static bike. Taking part involves one recording session in Building 45 at the University of Southampton, Highfield Campus. You will be asked to sit quietly for 5 minutes while we record your breathing noninvasively (no mouthpieces or facemasks). Then exercise on a static bike for 10 minutes, followed by more breathing pattern recording. The whole session will last about **30-40 minutes**.

For further information please contact: Mr Panagiotis (Panos) Sakkatos
PhD Student
Faculty of Health Sciences
University of Southampton
ps4e13@soton.ac.uk or 07492315767

Ethics NO: 18396 Version Number (2) Date: 20th November 2015

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Participant Information Sheet (PIS)

Study title: Validation of Structured Light Plethysmography compared to Respiratory Inductive Plethysmography in adults.

Researcher: Panagiotis Sakkatos, PhD student

You are being invited to take part in this research study. Before you decide whether you would like to participate in this research, please read carefully this information sheet to understand the aim of this research and what it will involve. If you are happy to participate you will be asked to sign a consent form. Please discuss it with others if you wish. Please do not hesitate to contact me if there is any more information that you would like, or if anything is unclear.

What is the purpose of this study?

Everyone breathes differently, with their own breathing pattern. We believe that breathing pattern give useful information about a person's lung health, but it is a very difficult thing to measure. In this research we want to test a relatively new device called Structured Light Plethysmography (SLP), to see if it is suitable for recording breathing patterns. SLP is a "contactless" measurement that uses cameras and reflected light to record movements of your chest wall.

Why I have been chosen?

You have been chosen because you are 18 years old or over, with no problems that might prevent you from pedaling a static exercise bike. We would like to record breathing patterns from about 50 people like you, using both the SLP and another recording device called Respiratory Inductive Plethysmography (RIP) at the same time, to see if they give similar measurements.

Do I have to take part in this research?

It is entirely up to you whether or not you would like to be a participant in this study. Please feel free to decide if you want to take part in this study and if yes, you are kindly requested to sign a consent form. Also you are able to withdraw from the study at any time during this research without giving any specific reason.

What will happen to me if I choose to take part in the research?

If you decide that you would like to take part in this study, you will be invited to attend a single recording session at the Faculty of Health Sciences Building 45 of the Highfield Campus at the University of Southampton. The recording session will take place in the Research Laboratory 0003 at Building 45 and will last approximately 30-40 minutes. When you arrive, you will have the study explained to you again, and you will be asked to sign a Consent Form. After this the researcher will ask you some questions relating to your age, gender, height, weight and general health. After that, you will be asked to blow hard into a tube to measure your lung volume. This will be done three times.

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For the breathing pattern recording, you will be asked to take off some of your outer garments (if you are female you will keep your undergarments on) and to stay with your own thin garment. Also you will be asked to put on an additional close-fitting white stretchy T-shirt. You will be able to dress/undress in privacy in the laboratory. Please feel free to bring a friend/relative with you if you believe that this would make you more comfortable during the recording session.

A tape measure will be placed around your chest to determine the appropriate size of recording equipment to use. You will then be asked to sit in a high-back chair and two stretchy bands will be placed around your chest and abdomen, over your own garment and below the white T-shirt. You will be asked to sit still and remain quiet during the recording period of 5 minutes. At the beginning of each recording period, you will be asked to take a deep breath and hold it for 5 seconds and then to breathe normally. This allows us to synchronise our two recording devices. After the first recording session in sitting, you will be asked to sit on a static bike and pedal for about 10 minutes. The resistance of the bike may gradually be made harder as you pedal, depending on your fitness.

After 10 minutes of pedaling, you will again be asked to sit in the high backed chair and your breathing pattern will be recorded for another 5 minutes. You will then be able to remove the bands and the T-shirt and be free to go. If you are interested we can show you images of your breathing patterns before you leave.

What are the side effects of breathing pattern recording?

This is a contactless measurement being compared to a noninvasive measurement. There are no known side-effects from either device. Both devices are commercially available and currently in use in clinics and research. There is a small potential risk from exercising on a static bike, but you will be supervised at all times and will not be asked to exercise maximally.

What are the possible disadvantages in taking part in this study?

There are no potential disadvantages in taking part in this research, beyond the small risk of exercising on a static bike. If you feel uncomfortable at any time, you can stop the exercise. If you have a respiratory problem that you know to be affected by exercise you are advised to bring any routine medication (you may use) with you to the recording session.

What are the possible benefits of taking part in this research?

There are no benefits to you personally from taking part in this study. You may find it interesting to measure your lung volume and see images of your breathing pattern. We hope that the information we collect will be useful to decide if the new device has potential for measuring breathing patterns in patients in the future.

Will my participation in this study be kept confidential?

All information collected during this research process will remain confidential. Data relating to breathing pattern will be anonymized (have your name removed) and stored in files in a laptop locked by a password. All other data will also be

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anonymized and coded to ensure your information will not be able to be identified. Personal information and signed consent forms will be securely stored in a locked cabinet within the University of Southampton in accordance with the policy of the University.

What to do if you want to complain?

If you have a concern or a complaint about this study you should contact the Research Governance Office (Address: University of Southampton, Building 37, Highfield, Southampton, SO17 1BJ; Tel: +44 (0)23 8059 5058; E-mail rgoinfo@soton.ac.uk. If you remain unhappy and wish to complain formally the Research Governance Office can provide you with details of the University of Southampton Complaints Procedure.

Where can I get more information?

If you would like to ask any more information about the study please contact Panagiotis Sakkatos at ps4e13@soton.ac.uk

Thank you for taking your time to read this information Sheet.

Contact details:

Researcher
Panagiotis Sakkatos
PhD student
Faculty of Health Sciences
University of Southampton
SO17 1BJ
ps4e13@soton.ac.uk

Supervisors
Prof Anne Bruton
Professor of Respiratory Rehabilitation
Faculty of Health Sciences
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SO17 1BJ
ab7@soton.ac.uk

Prof Anna Barney
Professor of Biomedical Acoustic Engineering
Faculty of Engineering and Environment
University of Southampton
SO17 1BJ
ab3@soton.ac.uk

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Screening Sheet

(To be completed by the researcher)

Date: ..... **Participant ID:** .....

Respiratory History

Have you ever been diagnosed with any disease affecting your breathing or lungs? YES ☐ NO ☐

If yes, what disease have you been diagnosed with?

.....

If yes, who made the diagnosis?

.....

If yes, do you take any kind of medication? YES ☐ NO ☐

If yes, what kind of medication do you take (name of the medication or description such as preventers/relievers)?

.....

If yes, how many times per day/per week do you take the medication?

.....

Do you have any cold or flu symptoms today? YES ☐ NO ☐

Musculoskeletal History

Do you have any problem that could affect your ability to pedal a static bike? YES ☐ NO ☐

If yes, what is it:

.....

Heart History

Have you ever been diagnosed with a heart problem by a medical practitioner? YES ☐ NO ☐

If yes, what is this problem?

.....

Ethics NO: 18396 Version Number (1) Date: 20th November 2015

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Consent Form (Version number 1)

PhD Study title: Validation of Structured Light Plethysmography compared to Respiratory Inductive plethysmography in adults

Researcher name: Panagiotis Sakkatos, PhD candidate

Ethics reference: 18396

Please initial the boxes if you are agree with the statement(s)

1) I confirm that I have read and understand the participant information sheet (20th November 2015/ version number 1) and have had the opportunity to ask questions about this study. ☐

2) I agree to take part in this research project and agree for my data to be used for the purpose of this study. ☐

3) I confirm that I have understood that my participation is voluntary and that I am free to withdraw at anytime, without justifying my decision and my legal rights being affected. ☐

4) I understand that my data may be looked only by responsible individuals involved in this research. I give permission for these individuals to have access to my research records. The "validity" of my consent is conditional upon the University complying with the Data Protection Act. ☐

(Full Name of participant)	(Date)	(Signature)
(Full Name of researcher)	(Date)	(Signature)

Ethics No: 18396 Version number (1) Date: 20th November 2015

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Demographic Data Sheet

(To be completed by the researcher)

Date: ..... **Participant ID:** .....

Gender: Male ☐ Female ☐

Age: .....years

Height (in meters): .....

Weight (in kilos): .....

Ethnicity: .....

Table of Lung Function Data

1st Attempt

Variables from Spirometry	Values (in Litres)
FVC	
Predicted FVC	
FEV_1	
Predicted FEV_1	
PEF	
Predicted PEF	
FEF	
Predicted FEF	

2nd Attempt

Variables from Spirometry	Values (in Litres)
FVC	
Predicted FVC	
FEV_1	
Predicted FEV_1	
PEF	
Predicted PEF	
FEF	
Predicted FEF	

Ethics No: 18396 Version number (1) Date: 20th November 2015

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3rd Attempt

Variables from Spirometry	Values (in Litres)
FVC	
Predicted FVC	
FEV_1	
Predicted FEV_1	
PEF	
Predicted PEF	
FEF	
Predicted FEF	

Ethics No: 18396 Version number (1) Date: 20th November 2015

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Borg Scale of Perceived Exertion for Exercise and Dyspnea

(completed by the researcher)

Classification	Descriptor
0	Rest
1	Very, very easy
2	Easy
3	Moderate
4	Somewhat hard
5	Hard
6	
7	Very hard
8	
9	Very, very hard
10	Maximum

For Shortness of breath

Rating	Intensity of Sensation
0	No symptoms
0.5	Very, very slight sensation of symptoms
1	Very Slight
2	Slight
3	Moderate
4	Somewhat Severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe
10	Maximal

Ethic No: 18396 Version Number (1) Date: 27th January 2016

B.2 Ethical approvals and materials used for participants' recruitment and data collection in the correlational study

Research Governance Feedback on your Ethics Submission (Ethics ID:27461)

ERGO <ergo@soton.ac.uk>
Παρ 4/8/2017 2:32 PM
Προς: Sakkatos P. <ps4e13@soton.ac.uk>

Submission Number 27461:
Submission Title The use of breathing patterns as a potential marker for asthma in adults:
The Research Governance Office has reviewed and approved your submission

You can begin your research unless you are still awaiting specific Health and Safety approval (e.g. for a Genetic or Biological Materials Risk Assessment) or external ethics review (e.g. NRES).The following comments have been made:

"

I am writing to confirm that the University of Southampton is prepared to act as Research Sponsor for this study under the terms of the Department of Health Research Governance Framework for Health and Social Care (2nd edition 2005). We encourage you to become fully conversant with the terms of the Research Governance Framework by referring to the Department of Health document which can be accessed at:

http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

If your study has been designated a Clinical Trial of an Investigational Medicinal Product, I would like to take this opportunity to remind you of your responsibilities under Medicines for Human Use Act regulations (2004/2006), The Human Medicines Regulations (2012) and EU Directive 2010/84/EU regarding pharmacovigilance If your study has been designated a 'Clinical Investigation of a Medical Device' you also need to be aware of the regulations regarding conduct of this work.

Further guidance can be found:

http://www.mhra.gov.uk/

The University of Southampton fulfils the role of Research Sponsor in ensuring management, monitoring and reporting arrangements for research. I understand that you will be acting as the Principal Investigator responsible for the daily management for this study, and that you will be providing regular reports on the progress of the study to the Research Governance Office on this basis.

Please also familiarise yourself with the Terms and Conditions of Sponsorship on our website, including reporting requirements of any Adverse Events to the Research Governance Office and the hosting organisation.

If your project involves NHS patients or resources please send us a copy of your NHS REC and Trust approval letters when available. Please also be reminded that you may need a Research Passport to apply for an honorary research contract of employment

from the hosting NHS Trust. Both our Terms and Conditions of Sponsorship and information about the Research Passport can be found on our website:

http://www.soton.ac.uk/corporateservices/rgo

Failure to comply with our Terms may invalidate your ethics approval and therefore the insurance agreement, affect funding and/or Sponsorship of your study; your study may need to be suspended and disciplinary proceedings may ensue.

Please do not hesitate to contact this office should you require any additional information or support. May I also take this opportunity to wish you every success with your research.

Submission ID : 27461
Submission Name: The use of breathing patterns as a potential marker for asthma in adults
Date : 04 Aug 2017
Created by : Panagiotis Sakkatos

"

Coordinator: Panagiotis Sakkatos

ERGO : Ethics and Research Governance Online
http://www.ergo.soton.ac.uk

DO NOT REPLY TO THIS EMAIL

Health Research Authority

Skipton House
80 London Road
London SE1 6LH

Tel: 0207 104 8010
Email: hra.approval@nhs.net

Mr Panagiotis Sakkatos
Faculty of Health Sciences, Building 45, Room 0059
Highfield Campus, University of Southampton
Southampton
SO17 1BJ

05 October 2017

Dear Mr Sakkatos

Letter of HRA Approval

Study title:	**The use of breathing patterns as a potential marker for asthma in adults**
IRAS project ID:	**230295**
Protocol number:	**27461**
REC reference:	**17/LO/1640**
Sponsor	**University of Southampton**

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

IRAS project ID	230286

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

IRAS project ID	230295

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **230295**. Please quote this on all correspondence.

Yours sincerely

Miss Helen Penistone
Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Diana Galpin (sponsor)*
Ms Emma Perry, Southampton General Hospital (lead NHS R&D)

University Hospital Southampton NHS
NHS Foundation Trust

Clinical Governance
R&D Department
SCBR Level E, Laboratory & Pathology Block
Mailpoint 138
Southampton General Hospital
Southampton
SO16 6YD

Tel: 023 8079 4245
Taru.Jussila-Knappett@uhs.nhs.uk

Panagiotis Sakkatos
Centre of Innovation and Leadership
Faculty of Health Sciences, Building 45,
Postgraduate Research Room 0059,
University of Southampton,
Highfield Campus
Southampton
SO17 1 BJ

15 February 2018

Dear Panagiotis Sakkatos,

Letter of access for research
(Multiple research projects (including RHM MED1477) involving data collection and consent with no likely impact on diagnosis or treatment)

This letter confirms your right of access to conduct research through **University Hospital Southampton NHS Foundation Trust (UHS)** for the purpose and on the terms and conditions set out below. This right of access commences on **15 February 2017** and ends on **1 November 2020** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **UHS** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **UHS** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **UHS**, you will remain accountable to your employer **(University of Southampton)** but you are required to follow the reasonable instructions of **Dr Hans Michael Haitchi or in Welcome Trust- Dr Kurukulaaratchy** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **UHS** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **UHS** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on UHS premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

UHS will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

I also enclose a copy of this letter for you to forward on to your employer's HR Department.

Yours sincerely,

Taru Jussila-Knappett
Research Governance Officer

[REC No:17/LO/1640] [IRAS ID:230295]
[26/09/17] [V2]

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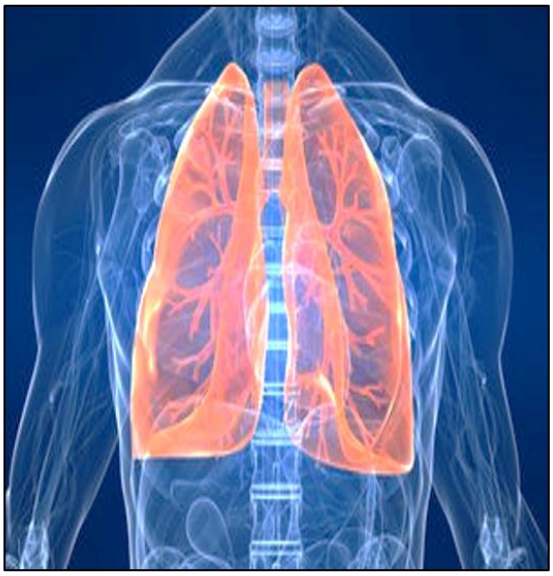
UNIVERSITY OF Southampton School of Health Sciences

What do you know about your breathing?

Are you aged 18 or over with asthma?

We are looking for adult volunteers with asthma to attend one session to measure your breathing patterns



What is involved?

- We will ask you to wear a white T-shirt
- 5 minutes sitting down with a light shone on your chest
- The purpose of the light is to measure your breathing
- Filling in 4 short questionnaires
- Blowing hard into a tube (3 times)
- The whole session lasts about 30-35 minutes

Where does the study takes place?

Wellcome Trust Research Facility, C Level West Wing, Southampton General Hospital.

For further information, please contact: Mr Panagiotis (Panos) Sakkatos, PhD student, University of Southampton
Tel: 07492315767
E-mail: ps4e13@soton.ac.uk

ps4e13@soton.ac.uk 07492315767

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Invitation Letter

Title of the study: The use of breathing patterns as a potential marker for asthma in adults

REC No:17/LO/1640 IRAS ID: 230295

This is an invitation to take part in a research study. You are receiving this letter and information because we believe you are aged 18 or over and have been diagnosed with asthma. My name is Panagiotis (known as Panos) Sakkatos, and I am a physiotherapist and a postgraduate student at the University of Southampton. I am carrying out a study about asthma as part of my PhD, which aims to explore whether breathing patterns can be used as a new way to give us information about your asthma.

I have enclosed a copy of a Participant Information Sheet for you to read. This will tell you about the study and help you decide if you wish to take part. If you do choose to take part in this study, you will be asked to meet me (the researcher) on one occasion, to take some measurements of your breathing. This appointment will take approximately 30-35 minutes.

You can contact me using any of the ways described in the information sheet (email, phone call or text). I look forward to hearing from you.

Yours sincerely,

Panagiotis (Panos) Sakkatos, MSc, BSc Physiotherapist

PhD candidate
Faculty of Health Sciences
Building 45, University of Southampton,
Southampton, SO17 1BJ
Tel: 07492315767
E-mail: ps4e13@soton.ac.uk

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Participant Information Sheet (PIS)

Study Title: The use of breathing patterns as a potential marker for asthma in adults

Researcher: Panagiotis (Panos) Sakkatos, PhD candidate, University of Southampton
REC NO:17/LO/1640 IRAS ID:230295

You are being invited to take part in a research study. Please take time to read the following information carefully before deciding to take part. It is important that you understand the purpose of the study and what it involves if you wish to take part. It is then up to you to decide whether or not to take part. If you are happy to take part you will be asked to sign a consent form when you meet the researcher. Please discuss this study with others if you wish.

Please contact the researcher if you have any questions about the study, or if anything here is unclear.

What is the research about?

This research is about finding out whether breathing patterns can be used to give us useful information about your asthma.

Why have I been asked to participate?

You have been approached because we believe you are aged 18 years old (or over) and have been diagnosed with asthma. We need around 200 people like you to complete our study.

Do I have to take part?

It is entirely your decision whether or not you would like to take part in this study. If you do decide to take part, you will be asked to fill in and sign a consent form. You can withdraw from the study at any time without giving us any reason. Your decision and participation in this study will not affect your current or future health care in any way.

If you have given informed consent but lose capacity to consent before or during the recording session, you will be withdrawn from the study. Any collected data will not be retained to be used for analysis.

What will happen to me if I choose to take part in the study?

If you would like to take part in this study, you will be invited to meet me (the main researcher - Panos Sakkatos) on one occasion. This meeting takes place at Southampton General Hospital. If you have any other hospital appointments we can try to arrange the meeting on the same day. The meeting with me will last about 20-30 minutes. When you arrive, I will explain the study and you will have the chance to ask any further questions. If you are still happy to take part, then I will ask you to fill in and sign a consent form, and give you a copy to take away.

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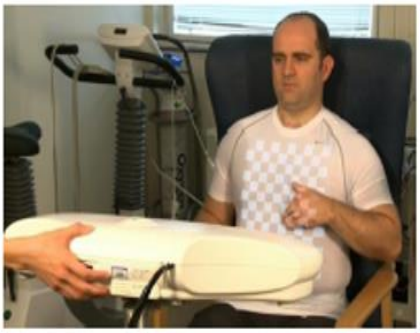
After this, I will ask you about your age, gender and any medicines/ puffers you may take for your asthma. I will measure your height and weight. I will then ask you to fill in some short questionnaires about your asthma, and your general wellbeing.

I will then ask you if you are happy to replace your upper body clothing with a close-fitting white T-shirt (we have all sizes available). This white T-shirt helps us to get good measurements of your breathing. You will be able to change in private and females will be able to retain any undergarments. If you have a thin vest, or similar, our T-shirt can be placed over the top of it. Please feel free to bring a friend or a family member, if this would help you to feel more comfortable. I will then measure your breathing pattern while you sit in a chair for 5 minutes.



This photo shows someone getting ready to have his breathing measured. He is sitting in the chair in his white T-shirt and the machine shines a light onto his chest in the form of a grid pattern (like a chess board). He has put his fingers at the end of his breast-bone to help me line up the machine correctly. While I record your breathing pattern, you will be asked to sit still and not talk for 5 minutes with the recording equipment positioned in front of you and a light shining onto your chest. You will not feel anything while your breathing pattern is being measured, and no radiation is used.

After the breathing pattern measures you will be able to change back into your normal clothes and you will be asked to carry out a lung function test using a hand-held spirometer. For this, you will be asked to blow as hard as you can, for as long as possible, into a tube. You will be asked to blow hard three times. (If you have recently done this test and we can access the results, then you may not need to do it again). I will then answer any questions you may have and you will be free to go.

Are there any benefits in my taking part?

There are no benefits for you personally from taking part in this study, although you may find it interesting to see your breathing pattern being modelled as a 3-D image by the machine. We hope that the information gained by this research will help us understand more about the relationship between breathing patterns and asthma, which in future may help us improve the way we monitor and manage it.

What are the side effects of breathing pattern recording?

There are no known side effects from breathing pattern recording. This is a contactless measurement and the device is commercially available and currently in use in NHS clinical settings and for research.

What are the possible disadvantages in taking part in this study?

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There are no known disadvantages or risks in taking part in this study. It is theoretically possible that the blowing task (lung function test) could aggravate some asthma symptoms such as coughing, but short-breaks will be taken after each attempt, and if you feel uncomfortable at any time during the lung function test, you can stop the procedure. ***Please bring any routine medication/ puffers with you.***

What should I do if I want to take part?
Please feel free to take as long as you wish to decide whether you want to take part in this study. If you choose to take part, please contact the researcher, Panagiotis (Panos) Sakkatos) through email, phone number, text or the reply slip, to indicate your interest for the study. Once you have contacted me, I will ask you a few questions to check whether you are suitable to take part in this study and I will arrange a mutually convenient appointment to meet you.

Will my participation in this study be kept confidential?
Your participation and the information we collect about you during the course of the research will be kept strictly confidential. Any information obtained by the questionnaires will be anonymised (have your name removed) and will be given an individual code. As a result, you will not be able to be identified. Consent forms and questionnaires will be securely stored in a locked filing cabinet within the research office (Building 67) at the University of Southampton in accordance with the policy of the University or any other required local authority of this study. Information relating to breathing patterns will be also anonymised and directly stored into files within the software of the device, which is password protected and only accessible by the researcher and his research team. This information will be also stored on the researchers' password protected laptop and a university computer to back it up.

Only members of the research team and responsible members of the University of Southampton may be given access to data about you for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

Who will have access to my medical records?

If you consent, the main researcher, Panagiotis (known as Panos) Sakkatos, will have access to your medical records during the study. His PhD supervisors, Prof Anne Bruton and Prof Anna Barney will have access only to anonymised data for the purposes of the study.

What will happen to the results of the research?
Your personal details will remain strictly confidential. All the information obtained for this study will be converted into figures for analysis. During the study all data from this study will be shared only by the researcher and his supervisors, Prof. Anne Bruton and Prof. Anna

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Barney. The data will be used only for the purposes of this study. After the study is completed, anonymised, unidentifiable data will be stored on an Open Access database (PURE) in line with university policy. The results of the study may be written up in the form of reports, chapters of a PhD thesis, or research articles published at conferences or in academic journals. Some of the information may be also used to develop future research ideas. Due to the anonymity of the data, you will not be able to be identified. If you would like a summary of the results, I can send you one after the study is completed.

What are the insurance/indemnity arrangements?
University of Southampton holds insurance policies which apply to this study. In the unlikely event that you experience physical harm as a result of your participation in this study, you may be able to claim compensation. For furher information, please contact the Research Governance office of University of Southampton (Address: University of Southampton, Building 37, Highfield, Southampton, SO17 IBJ; Tel: +44 (0)2380595058; E-mail rgoinfo@soton.ac.uk.)

Who has reviewed the study?
The study has been reviewed by the London-Queen Square Research Ethics Committee and Research Governance Office of University of Southampton.

What to do if you want to complain about the study?

If you have a concern about any aspect of this study, you should speak to the researcher (Panos) who will do his best to answer your questions.
If you remain unhappy or have a complaint about any aspect of this study, please contact the University of Southampton Research Integrity and Governance Manager (023 8059 5058, rgoinfo@soton.ac.uk).

Where can I get more information?
If you would like to ask any more information about the study, please contact Panagiotis (Panos) Sakkatos at ps4e13@soton.ac.uk.

Data Protection Privacy Notice
The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the researcher if you have any questions or are unclear what data is being collected about you.

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Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for 10 years after the study has finished after which time any link between you and your information will be removed. Also NHS will keep identifiable information about you from this study for 10 years after the study has finished.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

Thank you for taking your time to read this Information Sheet

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Contact details:
Researcher
Panagiotis (Panos) Sakkatos
PhD Student
Faculty of Health Sciences
University of Southampton
SO17 1BJ
Tel: 07492315767
ps4e13@soton.ac.uk

Supervisors
Prof Anne Bruton
Professor of Respiratory Rehabilitation
Faculty of Health Sciences
University of Southampton
SO17 1BJ
ab7@soton.ac.uk

Prof Anna Barney
Professor of Biomedical Acoustics
Faculty of Engineering and Environment
University of Southampton
SO17 1BJ
ab3@soton.ac.uk

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Screening Sheet

(To be completed by the researcher)

Date: ..... **Participant ID: .....**

Have you ever been diagnosed with asthma as determined by a respiratory clinical practitioner? YES ☐ NO ☐

Have you taken any medication for your asthma during the past 2 months? YES ☐ NO ☐

Have you been diagnosed with any other chronic respiratory problem? YES ☐ NO ☐

If yes, what disease have you been diagnosed with?

.....

Have you had any chest infection during the past week or at present? YES ☐ NO ☐

Have you had allergic rhinitis during the past week or at present? YES ☐ NO ☐

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CONSENT FORM

Study title: The use of breathing patterns as a potential marker for asthma in adults

Researcher name: Panagiotis (Panos) Sakkatos, PhD candidate, MSc, BSc physiotherapist
REC No:17/LO/1640
IRAS ID: 230295

Please initial the boxes if you agree with the statement(s):

I have read and understood the information sheet (8th November 2018/*version no 4*) and have had the opportunity to ask questions about the study.	
I agree to take part in this research and agree for my data to be used for the purpose of this study. I understand that anonymised personal data will be looked at only by responsible individuals involved in this study. I give permission for these individuals to have access to my research records. The validity of my consent is conditional upon the University complying with the Data Protection Act.	
I understand that relevant sections of my medical notes and data collected during the study may be also looked at by individuals from regulatory authorities, from the research sponsor or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I agree to allow the researcher, Panagiotis Sakkatos, to have access to my medical records, for the purposes of this study only.	
I understand and confirm that my participation is voluntary and that I may withdraw at any time for any reason, without my rights being affected.	

Name of participant ……

Signature of participant ……

Name of the researcher……..

Signature of the researcher……

Date……..

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Case Report Form

(To be completed by the researcher)

Study title: *The use of breathing patterns as a potential marker for asthma in adults*

Researcher's name: Panagiotis (Panos) Sakkatos, PhD candidate, University of Southampton

Researcher's supervisors: Prof Anne Bruton and Prof Anna Barney, University of Southampton

PARTICIPANT ID				

DATE OF RECORDING SESSSION						

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Demographic Data

Age .....

Gender: Female ☐ Male ☐

Weight (kg): .....

Height (cm): .....

Ethnicity: .....

What was your age when you were firstly diagnosed with asthma? ☐

What asthma phenotype were you diagnosed with?

Allergic (atopic) phenotype ☐ Non allergic (non-atopic asthma) ☐

I don't know ☐

Medication Usage

Are you currently taking any medication for your asthma? YES ☐ NO ☐

If yes, what type of asthma medication are you taking?

Short-acting relievers ☐ Oral or inhaled corticosteroids ☐ Both ☐

If yes, what is the frequency with which you are taking short–acting relievers (state the number of puffs taken each day/week)?

Per day:

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.....

.....

Per week:

.....

.....

If yes, what is the dose of oral/inhaled corticosteroids that you are taking for your asthma per day/week?

Dose of oral/inhaled corticosteroids (mg) per day:

.....

.....

.....

Dose of oral/inhaled corticosteroids (mg) per week:

.....

.....

.....

If yes, have you taken your asthma medication today (prior the data collection)?

Yes ☐ NO ☐

- If yes what type of medication did you take?

Short-acting relievers ☐ Oral/Inhaled corticosteroids ☐ Both ☐

Questionnaires

Has the participant completed the following questionnaires?

Asthma Control Questionnaire YES ☐ NO ☐ If no, give a reason

.....

HADS YES ☐ NO ☐ If no, give a reason

.....

Nijmegen Questionnaire YES ☐ NO ☐ If no, give a reason

.....

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Mini-AQLQ YES ☐ NO ☐ If no, give a reason

.....

Lung Function Test

Spirometry	1st attempt	2nd attempt	3rd attempt
FEV_1 (L/min)			
FVC (L/min)			
FEV_1/FVC (%)			
PEF (L/min)			

Best values of lung function test: FEV_1 .....

FVC .....

FEV_1/FVC .....

PEF .....

Predicted value of: FEV_1 .....

FVC .....

FEV_1/FVC .....

PEF .....

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[29/09/17][V2] [REC No: 17/LO/1640] [IRAS ID: 230295]

Asthma Control Questionnaire (Juniper et al. ERJ 1999 14:902-7)

Please *circle* the number of the response that best describes how you have been during the past week.

a)	On average, during the past week, how often were you **woken by your asthma** during the night?	0	Never
		1	Hardly ever
		2	A few times
		3	Several times
		4	Many times
		5	A great many times
		6	Unable to sleep because of asthma
b)	On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?	0	No symptoms
		1	Very mild symptoms
		2	Mild symptoms
		3	Moderate symptoms
		4	Quite severe symptoms
		5	Severe symptoms
		6	Very severe symptoms
c)	In general, during the past week, how **limited were you in your activities** because of your asthma?	0	Not limited at all
		1	Very slightly limited
		2	Slightly limited
		3	Moderately limited
		4	Very limited
		5	Extremely limited
		6	Totally limited
d)	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0	None
		1	A very little
		2	A little
		3	A moderate amount
		4	Quite a lot
		5	A great deal
		6	A very great deal
e)	In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
		1	Hardly any of the time
		2	A little of the time
		3	A moderate amount of the time
		4	A lot of the time
		5	Most of the time
		6	All the time
f)	On average, during the past week, how **many puffs/inhalations of short-acting bronchodilator** (e.g. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0	None
		1	1-2 puff/inhalations most days
		2	3-4 puff/inhalations most days
		3	5-8 puffs/inhalations most days
		4	9-12 puffs/inhalations most days
		5	13-16 puffs/inhalations most days
		6	More than 16 puffs/inhalations most days.
g)	**To be completed by researcher** FEV1 prebronchodilator..... FEV1 predicted..... FEV1 percent predicted.....	0	>95% predicted
		1	95-90%
		2	89-80%
		3	79-70%
		4	69-60%
		5	59-50%
		6	>50% predicted

The Nijmegen Questionnaire

The Nijmegen questionnaire gives a broad view of symptoms associated with dysfunctional breathing patterns. It is only a preliminary guide to breathing training.

Please ring the score that best describes the frequency with which you experienced the symptoms listed

Symptom	Never	Seldom	Some-times	Often	Very often
Chest pain	0	1	2	3	4
Blurred vision	0	1	2	3	4
Dizziness	0	1	2	3	4
Confusion or loss of touch with reality	0	1	2	3	4
Fast or deep breathing	0	1	2	3	4
Shortness of breath	0	1	2	3	4
Tightness across chest	0	1	2	3	4
Bloated sensation in stomach	0	1	2	3	4
Tingling in fingers and hands	0	1	2	3	4
Difficulty breathing or taking deep breaths	0	1	2	3	4
Stiffness or cramps in fingers and hands	0	1	2	3	4
Tightness around the mouth	0	1	2	3	4
Cold hands or feet	0	1	2	3	4
Palpitations in the chest	0	1	2	3	4
Anxiety	0	1	2	3	4
Totals					

Grand Total Score

BREATHE

Participants Initials

Visit/Time point

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (UNITED KINGDOM)
SELF-ADMINISTERED

PATIENT ID _____

DATE _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2. Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4. Feel bothered by COUGHING?	1	2	3	4	5	6	7
5. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6. Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7. Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8. Have DIFFICULTY GETTING A GOOD NIGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7

BREATHE

Participants Initials

Visit/Time point

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (UNITED KINGDOM) SELF-ADMINISTERED

PATIENT ID _____

DATE _____

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** DOING THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
13. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

DOMAIN CODE:

Symptoms: 1, 4, 6, 8, 10
Activity Limitation: 12, 13, 14, 15
Emotional Function: 3, 5, 9
Environmental Stimuli: 2, 7, 11

THE H.A.D.S. QUESTIONNAIRE

This questionnaire is designed to help us know how you feel. Please read each item and **underline or circle** the reply which comes closest to how you have been feeling in the past week.

Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

Patient ID: _____

Date: _____//_____//_____

1. I feel tense or 'wound up':

   Most of the time

   A lot of the time

   From time to time

   Not at all

2. I still enjoy the things I used to enjoy:

   Definitely as much

   Not quite as much

   Only a little

   Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen?

   Very definitely and quite badly

   Yes, but not too badly

   A little, but it does not worry me

   Not at all

4. I can laugh and see the funny side of things:

   As much as I always could

   Not quite so much now

   Definitely not so much now

   Not at all

5. Worrying thoughts go through my mind:

   A great deal of the time

   A lot of the time

   From time to time, but not too often

   Only occasionally

6. I feel cheerful:

   Not at all

   Not often

   Sometimes

   Most of the time

7. I can sit at ease and feel relaxed:

   Definitely

   Usually

   Not often

   Not at all

8. I feel as if I am slowed down:

   Nearly all the time

   Very often

   Sometimes

   Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach:

   Not at all

   Occasionally

   Quite often

   Very often

10. I have lost interest in my appearance:

    Definitely

    I don't take so much care as I should

    I may not take quite as much care

    I take just as much care as ever

11. I feel quite restless as if I have to be on the move:

Very much indeed

Quite a lot

Not very much

Not at all

12. I look forward with enjoyment to things:

As much as I ever did

Rather less than I used to

Definitely less than I used to

Hardly at all

13. I get sudden feelings of panic

Very often indeed

Quite often

Not very often

Not at all

14. I can enjoy a good book or radio or TV programme:

Often

Sometimes

Not often

Very seldom

B.3 Ethical Approval and materials used for participants' recruitment and data collection in the responsiveness study

NHS
Health Research Authority

Email: hra.approval@nhs.net

2 June 2016

Dr Rokhsaneh Tehrany PhD, MSc, MCSP, BSc (HONS)
Post Research Fellow
University of Southampton
Room 0001, Building 45
Faculty of Health Sciences
Highfield Campus, University of Southampton
Post Code SO17 1BJ

Dear Dr Tehrany

Letter of HRA Approval for a study processed under pre-HRA Approval systems

Study title:	**Breathing pattern recordings before and after physiotherapy breathing retraining for asthma**
IRAS project ID:	**197059**
REC reference:	**16/SC/0083**
Sponsor	**University of Southampton**

Thank you for your request to bring the above referenced study under HRA Approval.

I am pleased to confirm that the study has been given **HRA Approval**, on the basis of the document set provided, any clarifications noted in this letter and taking account of reviews and approvals previously conducted and issued.

The extension of HRA Approval to this study on this basis allows the sponsor and NHS organisations to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

IRAS project ID	197059

After HRA Approval

In addition to the document, *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England. If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

Your IRAS project ID is 197059. Please quote this on all correspondence.

Yours sincerely

Isobel Lyle | Senior Assessor
Health Research Authority
HRA, Room 002, TEDCO Business Centre, Health Research Authority, Rolling Mill Rd, Jarrow NE32 3DT
Hra.approvals@nhs.net or Isobel.lyle@nhs.net
M: 07827 984549
www.hra.nhs.uk

Copy to:
Ms Diana Galpin, Southampton University
Ms Jennifer Peach, Southampton General Hospital
Professor Anne Bruton, Southampton University
LCRN: Wessex

University Hospital Southampton NHS
NHS Foundation Trust

Clinical Governance
R&D Department
SCBR Level E, Laboratory & Pathology Block
Mailpoint 138
Southampton General Hospital
Southampton
SO16 6YD

Tel: 023 8079 8591
Taru.Jussila-Knappett@uhs.nhs.uk

Panagiotis Sakkatos
Centre of Innovation and Leadership
Faculty of Health Sciences, Building 45,
Postgraduate Research Room 0059,
University of Southampton,
Highfield Campus
Southampton
SO17 1 BJ

28 July 2016

Dear Panagiotis Sakkatos,

Letter of access for research
(RHM* Med1324, *involving Non-invasive data collection for breathing pattern with no likely impact on diagnosis or treatment)

This letter confirms your right of access to conduct research through **University Hospital Southampton NHS Foundation Trust (UHS)** for the purpose and on the terms and conditions set out below. This right of access commences on **14 July 2016** and ends on **25 July 2017** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at **UHS** has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to **UHS** premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through **UHS**, you will remain accountable to your employer **(University of Southampton)** but you are required to follow the reasonable instructions of **Local Collaborator, Physiotherapist Charlotte Church** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **UHS** policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with **UHS** in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on UHS premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

UHS will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

I also enclose a copy of this letter for you to forward on to your employer's HR Department.

Yours sincerely,

Taru Jussila-Knappett
Research Governance Officer

Health Sciences

UNIVERSITY OF Southampton

Title: Breathing pattern recordings before and after physiotherapy breathing retraining for asthma

Ethics Number: 16/SC/0083

You are receiving this letter and information because you have been referred for physiotherapy to help you with your breathing. My name is Roxy Tehrany and I am carrying out a research study at the University of Southampton, which aims to look at how breathing patterns are affected by physiotherapy breathing retraining. I would like to invite you to take part in this study.

I have enclosed a copy of an Information Sheet that will provide you with more detailed information about the study and what taking part would involve for you. If you would like to take part in the study, I would like you to attend a maximum of three research appointments which will all take place on the same day as your scheduled appointments with the physiotherapist. Each research appointment will take approximately 45 minutes.

If you are interested in taking part, or would like further information, I would be grateful if you could complete the enclosed reply slip and post it to me using the pre-paid envelope provided. Or you can contact me directly via sending an email in which you will indicate your interest in this study. I will contact you as soon as I receive the reply-slip on the contact details that you provide or on your email sent by you to me. Alternatively, you can contact me, on 07492315767 for further information.

Whether you decide to take part or not will not affect your current or future treatment.

Yours sincerely,

Roxy Tehrany, PhD, MSc, BSc, MCSP

Research Fellow and Physiotherapist
Postgraduate Office,
Faculty of Health Sciences
University of Southampton,
Southampton
SO17 1BJ

Direct tel: 07492315767
email: ps4e13@soton.ac.uk

Health Sciences

UNIVERSITY OF Southampton

Reply slip

If you are interested in taking part in this study, or would like further information about it, please fill out this reply-slip. You can return it by post, using the pre-paid envelope, pre-addressed. The researcher will then contact you on the telephone number or email address that you provide.

Alternatively, you can contact the researcher directly on 07492315767 or ps4e13@soton.ac.uk for further information.

Your Name:.....

Your Telephone Number: .....

Your Email address (if preferred).....

Please indicate a convenient time and date for the researcher to

telephone you:.....

Thank you

Roxy Tehrany

Research Fellow

09/08/2016
V3

Health Sciences

UNIVERSITY OF Southampton

Participant Information Sheet (PIS)

Title: Breathing patterns in asthma

You are being invited to take part in a research study. Before you decide whether you would like to take part, it is important that you understand the purpose of the research and what it will involve if you wish to take part.

Please take time to read the following information and discuss it with others if you wish. It is important that you understand all of the information before you decide whether or not you would like to take part in the research.

Please contact us if there is any more information that you require or if anything is unclear.

What is the purpose of this study?

Physiotherapy breathing retraining is a form of treatment that can benefit some people with asthma, by helping them to control their breathing and reduce their asthma symptoms. At present, we do not know if, or how, this therapy affects people's breathing patterns. We would like to record your breathing pattern before and after a physiotherapy breathing retraining programme to see if there are any measurable changes.

Why have I been invited?

You have been approached because you have been referred for physiotherapy breathing retraining by your consultant. We would like to record breathing and speech patterns from a group of 48 people like you, before and after a physiotherapy breathing retraining programme.

Do I have to take part?

It is entirely your decision whether or not you decide to take part in this study. If you do decide to take part, you will be asked to sign a consent form. You are also free to withdraw from the study at any time without having to give a reason. This decision will not affect your current or future treatment in any way.

What will happen to me if I take part?

If you would like to take part in this study, you will be invited to attend a minimum of two, and maximum of three additional breathing pattern recording sessions. Each recording session will take approximately 45 minutes and these will take place on the same days as your breathing retraining appointments with the physiotherapist, just before the physiotherapy session.

When you arrive for your first recording session you will be given a chance to ask any questions you may have about the study, and will then be asked to fill in and sign a consent form. You will then be asked to give information about your age, gender and general health. We would also like to ask you about any medicines you may have taken. After this you will be asked to carry out some simple lung health tests. For these you will be asked to blow as hard as you can through a tube, for as long as possible. You will then be asked to wear a white t-shirt (which we will provide) while we record your breathing patterns. You will be given privacy while you change your clothing, and females may still wear their undergarments. Please feel free to bring a friend, or family member, if this would help you to feel more comfortable. To record your breathing patterns, we will ask you to remain seated while a breathing pattern recording device is positioned in front of you, and lights are shone onto your chest. This is why we will require you to wear a white t shirt, so that the lights can be clearly seen on your chest. You will not feel anything while your breathing patterns are being recorded because the technology is completely contactless. You will also be asked to wear a microphone so that we can record your speech patterns. This will be similar to the ones used by people working in call centres. We would then like to record your breathing for five minutes while you sit quietly, and for two minutes while you are talking. We will ask you to speak about any topic of your choice (for example, you could describe what you did the day before). Your voice will be recorded during this time so that we can examine what happens to your breathing patterns while you speak. We will not use these recordings for anything else before they are destroyed. After this the microphone will be removed, and replaced by a small tube placed near your nose to measure the air that you breathe in and out. You will be asked to complete some simple questionnaires about your health while wearing this tube. After that you will be able to remove the white t-shirt and you will be free to go to your breathing retraining appointment with the physiotherapist. We will make sure the physiotherapist knows when you are on your way.

What are the side effects of any treatment received when taking part in this study?
There are no known side effects to taking part in this study.

What are the possible disadvantages in taking part in this study?
There are no known disadvantages or risks in taking part in this study.

What are the possible benefits of taking part in this study?
There are no direct benefits for you personally from taking part in this study, although it may be interesting for you to see if your own breathing pattern changes at all. It is hoped that the information gained from this study may be used to gain knowledge about how breathing retraining affects patients. This could lead to improved understanding of who might benefit most from this type of therapy.

Will my taking part in this study be kept confidential?
All information collected during the research process will remain confidential. Any data that is collected from you will have your name removed and will be allocated with an individual

code so that you will not be able to be identified. The information will be stored on a password protected laptop that will be stored in a locked cupboard within the university.

What will happen to the results of the research study?

The information recorded from breathing and speech patterns will be converted into figures for analysis. Some of the information may be used to develop future research ideas. The findings may be written up in the form of reports or research articles and published at conferences or in academic journals. If this happens, you will not be identifiable. If you would like a copy of the research findings, we can send you a summary after the study is completed.

Who has reviewed the study?

The study has been reviewed by the South Central-Hampshire B Research Ethics Committee.

What to do if you want to complain.

If you have a concern or a complaint about this study you should contact the Research Governance Office (Address: University of Southampton, Building 37, Highfield, Southampton, SO17 1BJ
Tel: +44 (0)23 8059 5058
Email: rgoinfo@soton.ac.uk .
If you remain unhappy and wish to complain formally they can provide you with details of the University of Southampton formal Complaints Procedure.

Thank you for taking the time to read this Information Sheet

If you would like any further information please contact:

Roxy Tehrany PhD, MSc, MCSP
Research Fellow
ps4e13@soton.ac.uk
Tel: 07492315767

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Participant consent form

Patient Identification Number for this study:

Title of Project: Breathing pattern recordings before and after breathing retraining for adults with asthma.

Name of Researcher:

Please initial boxes:

1. I confirm that I have read and understand the information sheet dated 27.01.2016 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐

3. I understand that my data may be looked at by responsible individuals Involved in the study where it is relevant to my taking part in research. I give permission for these individuals to have access to my research records. ☐

4. I understand that the study will include the use of voice recordings, but nothing I say will appear in any research report or publication. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Faculty of Health Sciences, University of Southampton, Building 45, Highfield Campus, Southampton SO17 1BJ United Kingdom
Tel: +44 (0)23 8059 7979 Fax: +44 (0)23 8059 7900 www.southampton.ac.uk/healthsciences

16/03/2016 v2

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Breathing pattern recordings before and after breathing re-training for asthma

Case Report Form

Baseline only

Participant ID				

Participant Initials			

Date of Visit	D	D	M	M	y	Y

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Patient demographics

Day/Month/Year of Birth | M | M | M | Y | Y | Y | Age | | |

Sex Male ☐ Female ☐

Weight (Kg) ☐

Height (cm) ☐

Ethnicity ☐

Age first diagnosed with Asthma ☐

Medication usage

Currently taking any medication? ☐ Yes ☐ No

if 'yes' please provide the names of the medications you are currently taking, and the amount administered each day. If taking inhalers, please state the number of puffs taken each day

.....

.....

.....

.....

.....

.....

.....

.....

.....

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Questionnaires

Have the following questionnaires been completed:

All participants:

Nijmegen ☐ yes ☐ No –If no, give reason .....

Mini AQLQ ☐ yes ☐ No .....

HADs ☐ yes ☐ No .....

ACQ ☐ ye ☐ No.....

Breathing pattern recordings

Have breathing patterns been recorded during the following conditions:

Quiet breathing ☐ yes ☐ No (reason).....

Spontaneous speech ☐ yes ☐ No (reason).....

Breathing parameters during QUIET BREATHING:

	Values (full body)
RR	
TI/TE	
TI	
TE	
TI/Ttot	
Ttot	

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	Values	Overall phase	Principle angle	Spread
Ribcage				
Abdomen				
Left				
Right				
Upper left		n/a	n/a	n/a
Upper right		n/a	n/a	n/a
Lower left		n/a	n/a	n/a
Lower right		n/a	n/a	n/a

Breathing parameters during a SPONTANEOUS SPEECH TASK:

	Values (full body)
RR	
TI/TE	
TI	
TE	
TI/Ttot	
Ttot	

	Values	Overall phase	Principle angle	Spread
Ribcage				
Abdomen				
Left				
Right				
Upper left		n/a	n/a	n/a
Upper right		n/a	n/a	n/a
Lower left		n/a	n/a	n/a
Lower right		n/a	n/a	n/a

Spirometry:

	1st	2nd	3rd
FEV_1			
FVC			
FEV_1%			
PEFR			
FEV_1 predicted			
FEV_1% predicted			

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Breathing pattern recordings before and after breathing re-training for asthma

Case Report Form

Session 2

Participant ID				

Participant Initials			

Date of Visit	D	D	M	M	y	Y	

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Medication usage

Currently taking any medication? ☐ Yes ☐ No

if 'yes' please provide the names of the medications you are currently taking, and the amount administered each day. If taking inhalers, please state the number of puffs taken each day

.....

.....

.....

.....

.....

.....

.....

Frequency of practicing at home: ..... (per day)

Questionnaires

Have the following questionnaires been completed:

All participants:

Nijmegen ☐ yes ☐ No –If no, give reason

.....

Mini AQLQ ☐ yes ☐ No .....

HADs ☐ yes ☐ No .....

ACQ ☐ ye ☐ No.....

Breathing pattern recordings

Have breathing patterns been recorded during the following conditions:

Quiet breathing ☐ yes ☐ No (reason).....

Spontaneous speech ☐ yes ☐ No (reason).....

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Breathing parameters during QUIET BREATHING:

	Values (full body)
RR	
TI/TE	
TI	
TE	
TI/Ttot	
Ttot	

	Values	Overall phase	Principle angle	Spread
Ribcage				
Abdomen				
Left				
Right				
Upper left		n/a	n/a	n/a
Upper right		n/a	n/a	n/a
Lower left		n/a	n/a	n/a
Lower right		n/a	n/a	n/a

Breathing parameters during a SPONTANEOUS SPEECH TASK:

	Values (full body)
RR	
TI/TE	
TI	
TE	
TI/Ttot	
Ttot	

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	Values	Overall phase	Principle angle	Spread
Ribcage				
Abdomen				
Left				
Right				
Upper left		n/a	n/a	n/a
Upper right		n/a	n/a	n/a
Lower left		n/a	n/a	n/a
Lower right		n/a	n/a	n/a

Spirometry:

	1st	2nd	3rd
FEV_1			
FVC			
FEV_1%			
PEFR			
FEV_1 predicted			
FEV_1% predicted			

Appendix C Supplemental results of each study included in this research

C.1 Supplemental results of the SLP validation study

Table C1-1: Mean values of timing parameters as measured separately by the RIP and the SLP at rest in a sample of 50 adults

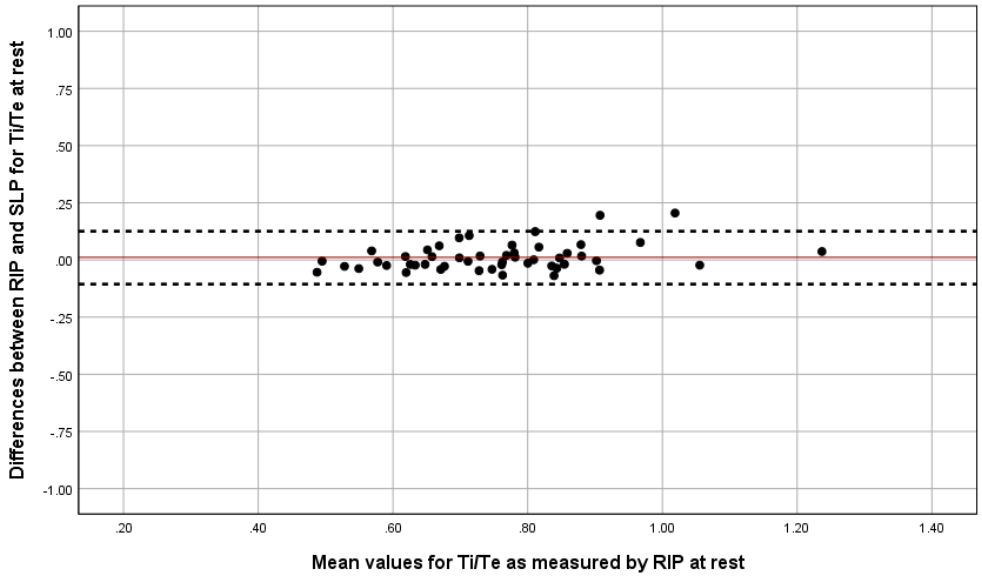
	RIP		SLP	
Breathing parameter	**μ* (sd)**	**95%CI* Lower-upper**	**μ (sd)**	**95%CI Lower-upper**
RR (bpm)	14.29 (3.92)	13.18 - 15.41	14.28 (3.92)	13.17 - 15.40
T_i (sec)	1.93 (0.59)	1.77 - 2.10	1.91 (0.56)	1.75 - 2.07
T_e (sec)	2.59 (0.77)	2.37 - 2.81	2.62 (0.79)	2.39 - 2.84
T_{tot} (sec)	4.52 (1.27)	4.16 - 4.89	4.53 (1.27)	4.17 - 4.89
T_i/T_e	0.75 (0.15)	0.71 - 0.79	0.74 (0.14)	0.70 - 0.78
T_i/T_{tot}	0.42 (0.47)	0.41 - 0.44	0.42 (0.44)	0.41 - 0.44

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals

Table C1-2: Mean values of timing parameters as measured separately by the RIP and the SLP after exercise in a sample of 50 adults

	RIP		SLP	
Breathing parameter	**μ* (sd)**	**95%CI* Lower-upper**	**μ (sd)**	**95%CI Lower-upper**
RR (bpm)	17.87 (4.77)	16.51 - 19.22	17.86 (4.75)	16.49 - 19.19
T_i (sec)	1.56 (0.45)	1.43 - 1.69	1.57 (0.42)	1.44 - 1.69
T_e (sec)	2.06 (0.66)	1.88 - 2.25	2.05 (0.67)	1.86 - 2.24
T_{tot} (sec)	3.62 (1.05)	3.32 - 3.92	3.62 (1.05)	3.32 - 3.92
T_i/T_e	0.77 (0.13)	0.73 - 0.80	0.78 (0.13)	0.74 - 0.82
T_i/T_{tot}	0.43 (0.04)	0.42 - 0.44	0.43 (0.04)	0.42 - 0.44

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals



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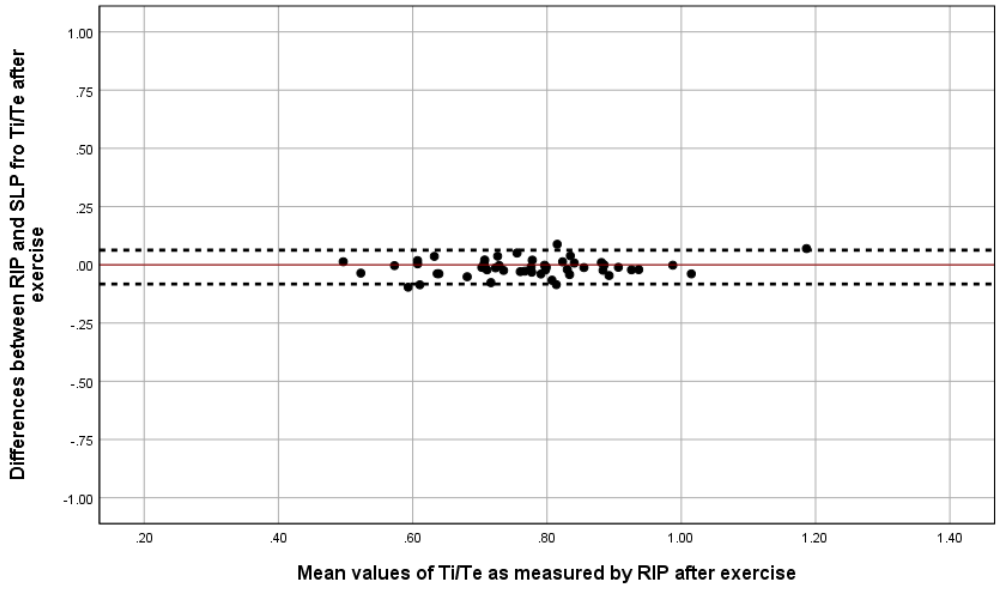
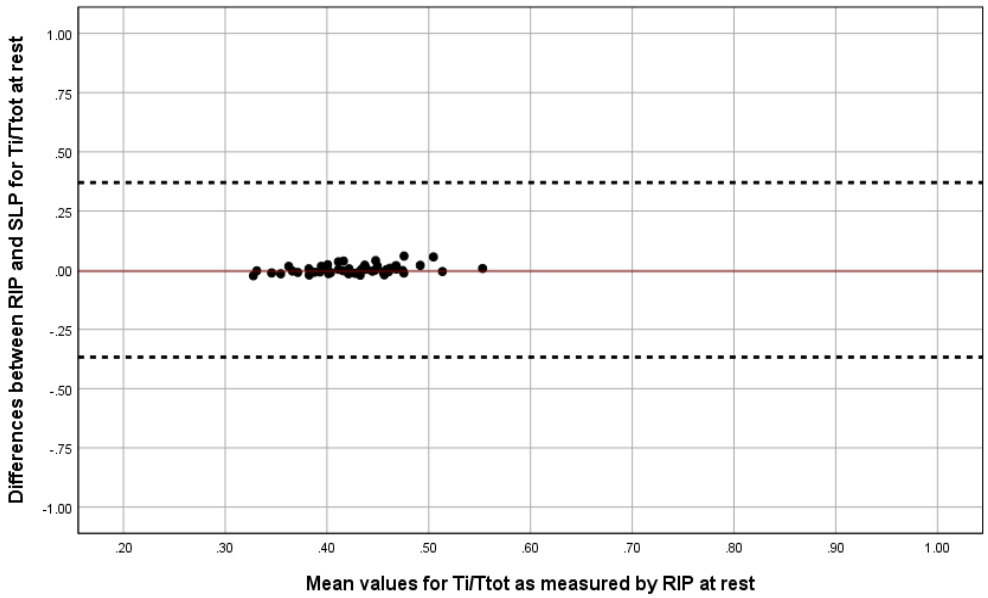
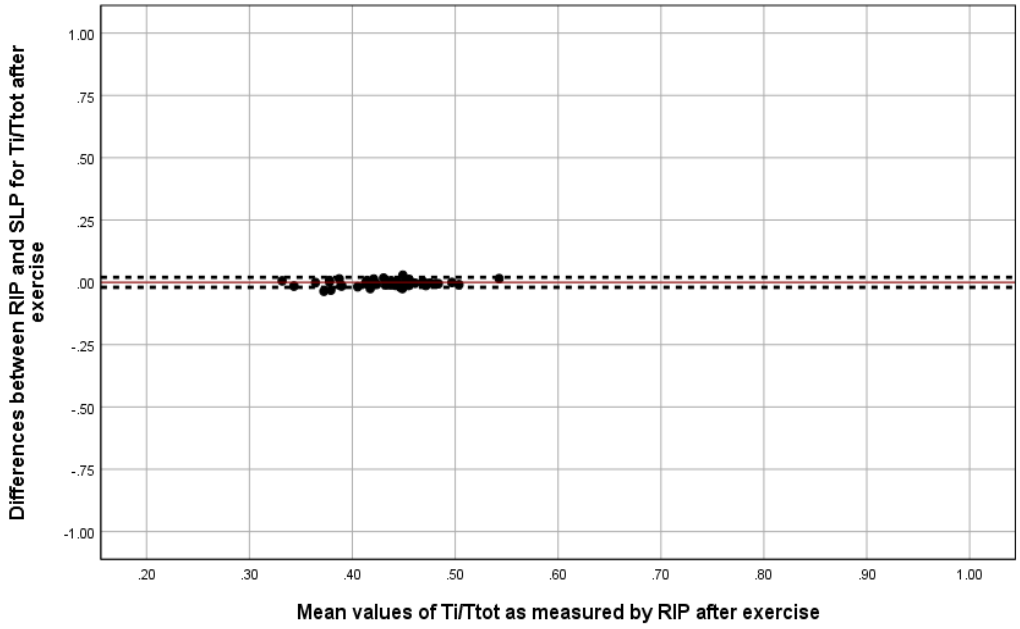


(b)

Figure C1-1: The Bland and Altman Plot for Ti/Te at rest (plot a) and after exercise (plot b)



(a)



(b)

Figure C1-2: The Bland and Altman plot for Ti/Ttot at rest (plot a) and after exercise (plot b)

Table C1-3: Mean differences in timing parameters between resting breathing and after exercise as measured by the RIP in a sample of 50 adults

Breathing parameters	**μ*** **(sd)**	**95%CI*** **Lower-upper bound**	**Sig.***
RR (bpm)	-3.57 (2.96)	-4.41 - -2.73	0.000
Ti (sec)	0.37 (0.35)	0.27 – 0.47	0.000
Te (sec)	0.53 (0.53)	0.38 – 0.68	0.000
Ttot (sec)	0.90 (0.83)	0.67 – 1.14	0.000
Ti/Te	-0.02 (0.09)	-0.04 – 0.01	0.231
Ti/Ttot	0.00 (0.03)	-0.01 – 0.00	0.163

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals; significance at p<0.01 after Bonferroni correction for multiple t-tests

Table C1-4: Mean differences in timing parameters between resting breathing and after exercise as measured by the SLP in a sample of 50 adults

Breathing parameters	**μ*** **(sd)**	**95%CI*** **Lower-upper bound**	**Sig.***
RR (bpm)	-3.57 (2.95)	-4.41 - -2.73	0.000
Ti (sec)	0.34 (0.34)	0.25 – 0.44	0.000
Te (sec)	0.56 (0.53)	0.41 - 071	0.000
Ttot (sec)	0.91 (0.83)	0.67 – 1.14	0.000
Ti/Te	-0.04 (0.08)	-0.06 - -0.01	0.102
Ti/Ttot	-0.01 (0.03)	-0.02 – 0.00	0.141

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals; significance at p<0.01 after Bonferroni correction for multiple t-tests

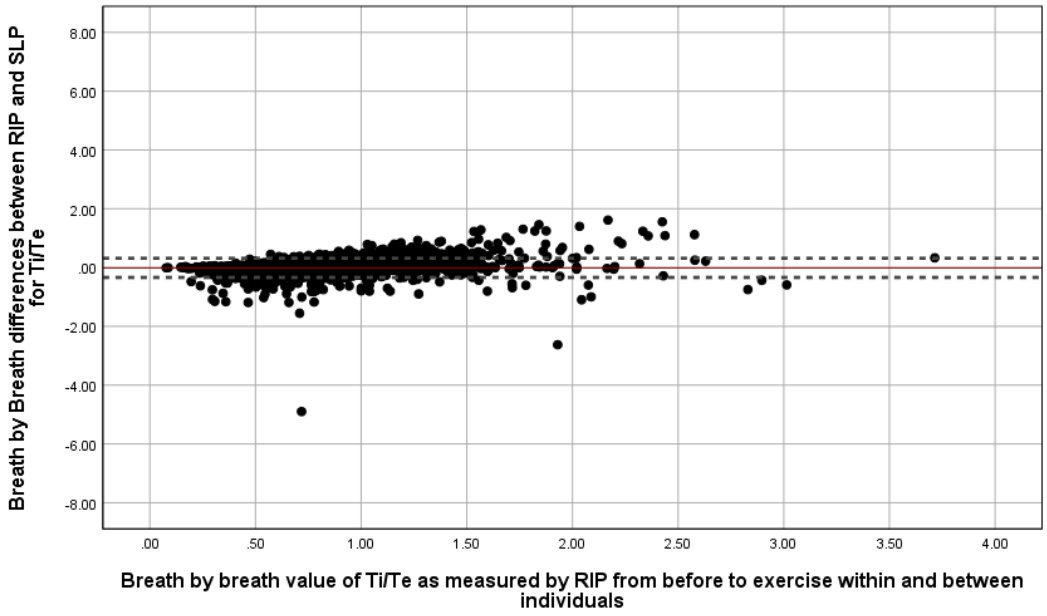


Figure C1-3: Breath-by-breath agreement between the RIP and the SLP for Ti/Te

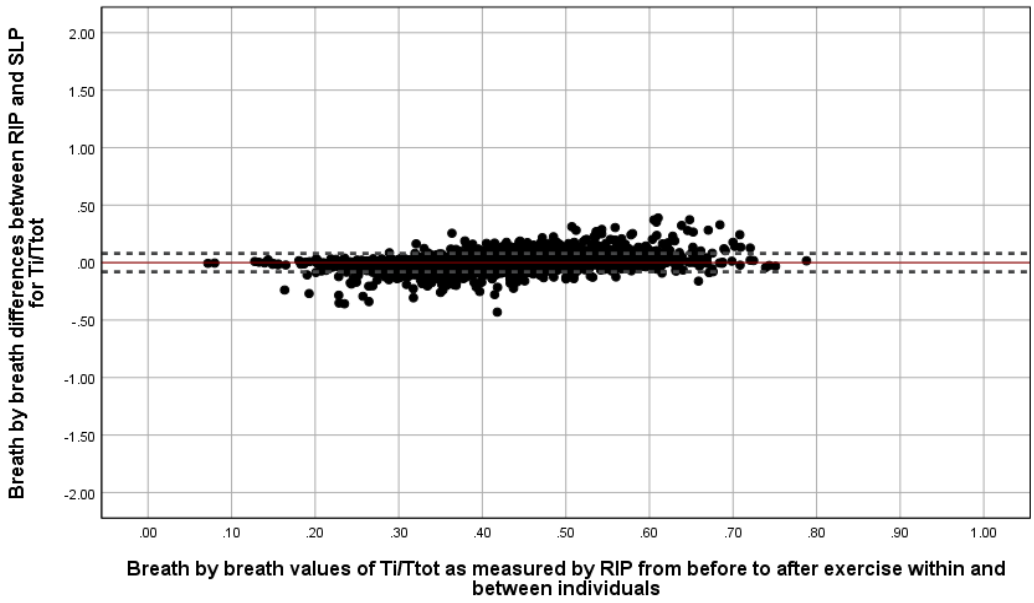


Figure C1-4: Breath-by-breath agreement between the RIP and the SLP for Ti/Ttot

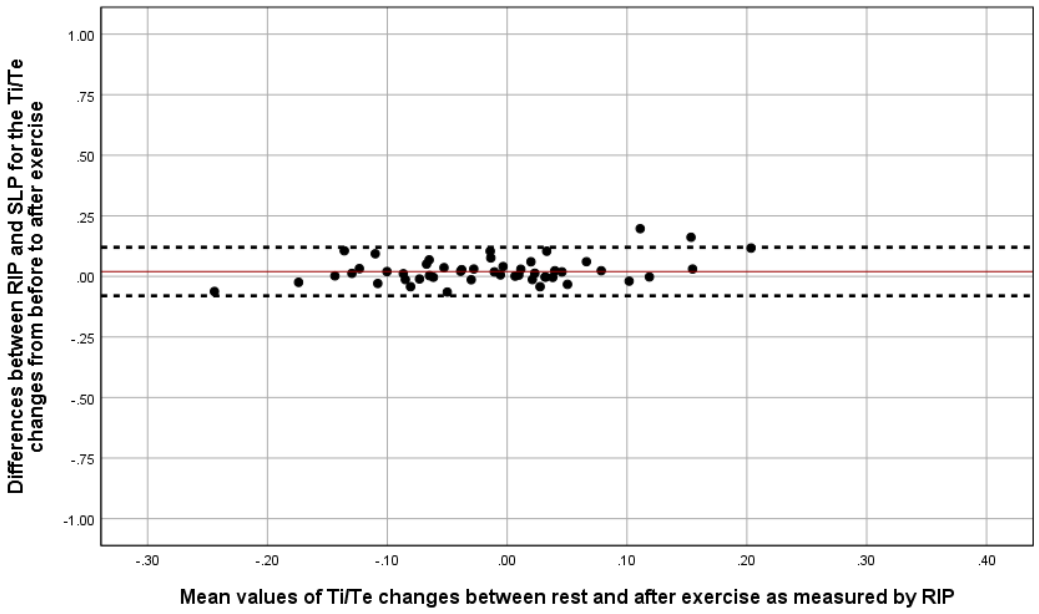


Figure C1-5: The agreement between the RIP and the SLP for the changes in Ti/Te between resting breathing and after exercise

Figure C1-6: The agreement between the RIP and the SLP for the changes in Ti/Ttot between resting breathing and after exercise

Table C1-5: Mean values of RC_{amp}, AB_{amp} and RC_{amp}/AB_{amp} during both respiratory phases as measured separately by the RIP and the SLP at rest in a sample of 50 adults

	RIP		SLP	
Breathing parameter	**μ* (sd)**	**95%CI* Lower-upper**	**μ (sd)**	**95%CI Lower-upper**
RC_{ampins} (arbitrary units)	0.83 (0.39)	0.72 – 0.94	0.52 (0.27)	0.45 – 0.60
RC_{ampexp} (arbitrary units)	0.83 (0.39)	0.72 – 0.94	0.53 (0.27)	0.45 – 0.61
AB_{ampins} (arbitrary units)	0.68 (0.25)	0.61 – 0.75	0.45 (0.18)	0.40 – 0.50
AB_{ampexp} (arbitrary units)	0.68 (0.25)	0.61 – 0.75	0.45 (0.18)	0.39 – 0.50
RC_{ampins}/AB_{ampins}	1.27 (0.53)	1.12 – 1.42	1.24 (0.49)	1.10 - 138
RC_{ampexp}/Ab_{ampexp}	1.27 (0.53)	1.12 – 1.42	1.24 (0.49)	1.10 – 1.38

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals

Table C1-6: Mean differences (plus 95%LOA) between the RIP and the SLP for the RC_{ampexp}, AB_{ampexp} and RC_{ampexp}/AB_{ampexp} at rest in a sample of 50 adults

Breathing parameter	**μ* (sd)**	**95%CI* Lower-Upper**	**95%LOA* Lower-upper**
RC_{ampexp} (arbitrary units)	0.31 (0.18)	0.25 – 0.36	-0.05 – 0.67
AB_{ampexp} (arbitrary units)	0.23 (0.15)	0.19 – 0.28	-0.06 – 0.52
RC_{ampexp}/AB_{ampexp}	0.03 (0.20)	-0.02 – 0.09	-0.37 – 0.43

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals: **95%LOA:** 95% limits of agreement

Table C1-7: Mean values of the RC_{amp}, AB_{amp} and RC_{amp}/AB_{amp} during both respiratory phases as measured separately by the RIP and the SLP after exercise in a sample of 50 adults

	RIP		**SLP**	
Breathing parameter	**μ* (sd)**	**95%CI* Lower-upper**	**μ (sd)**	**95%CI* Lower-upper**
RC_{ampins} (arbitrary units)	1.09 (0.42)	0.97 – 1.21	0.65 (0.24)	0.58 – 0.72
RC_{ampexp} (arbitrary units)	1.08 (0.40)	0.97 – 1.20	0.65 (0.24)	0.58 – 0.72
AB_{ampins} (arbitrary units)	0.81 (0.27)	0.73 – 0.88	0.52 (0.21)	0.47 – 0.57
AB_{ampexp} (arbitrary units)	0.80 (0.27)	0.73 – 0.88	0.52 (0.19)	0.47 – 0.57
RC_{ampins}/AB_{ampins}	1.43 (0.50)	1.28 – 1.57	1.33 (0.47)	1.19 – 1.46
RC_{ampexp}/AB_{ampexp}	1.42 (0.50)	1.28 – 1.56	1.33 (0.48)	1.19 – 1.47

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals

Table C1-8: Mean differences (plus 95%LOA) between the RIP and the SLP for the RC_{ampexp}, AB_{ampexp} and RC_{ampexp}/AB_{ampexp} after exercise in a sample of 50 adults

Breathing parameter	**μ* (sd)**	**95%CI* Lower-Upper**	**95%LOA* Lower-upper**
RC_{ampexp} (arbitrary units)	0.43 (0.27)	0.35 – 0.51	-0.11 – 0.97
AB_{ampexp} (arbitrary units)	0.28 (0.19)	0.23 – 0.33	-0.09 – 0.65
RC_{ampexp}/AB_{ampexp}	0.09 (0.25)	0.02 – 0.16	-0.39 – 0.57

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals: **95%LOA:** 95% limits of agreement

Table C1-9: Mean differences in RC_{amp}, AB_{amp} and RC_{amp}/AB_{amp} during both respiratory phases between resting breathing and after exercise as measured by the RIP

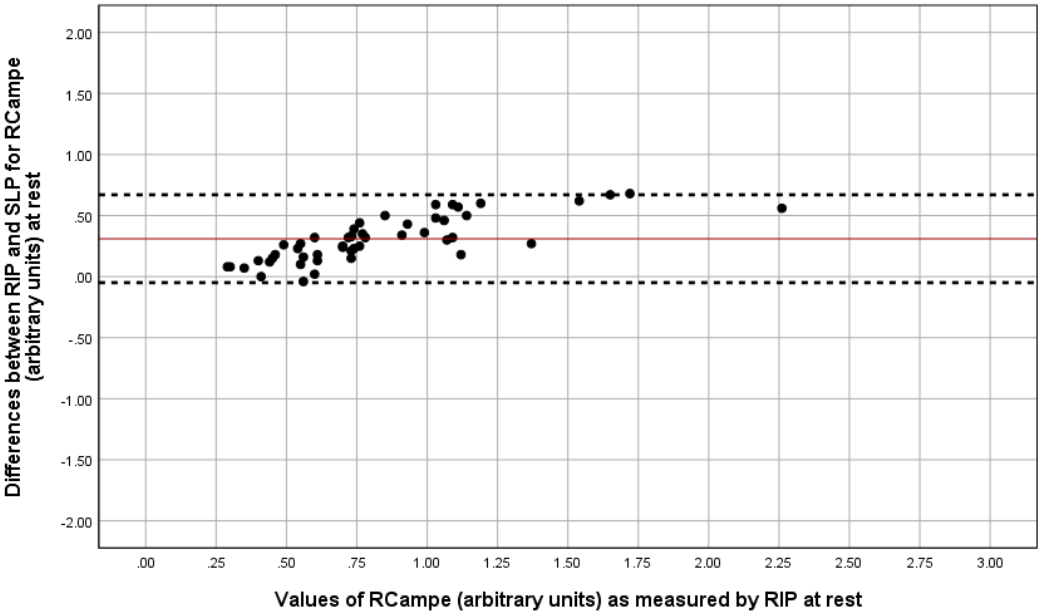
Breathing parameters	**μ (sd)**	**95%CI Lower-upper bound**
RC_{ampins} (arbitrary units)	-0.26 (0.28)	-0.18 - -0.35
RC_{ampexp} (arbitrary units)	-0.25 (0.29)	-0.17 - -0.34
AB_{ampins} (arbitrary units)	-0.12 (0.20)	-0.18 – -0.07
AB_{ampexp} (arbitrary units)	-0.12 (0.19)	-0.18 - -0.07
RC_{ampins}/AB_{ampins}	-0.15 (0.42)	-0.27 - -0.03
RC_{ampexp}/Ab_{ampexp}	-0.15 (0.42)	-0.27 - -0.03

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals

Table C1-10: Mean differences in RC_{amp}, AB_{amp} and RC_{amp}/AB_{amp} during both respiratory phases between resting breathing and after exercise as measured by the SLP

Breathing parameters	**μ (sd)**	**95%CI Lower-upper bound**
RC_{ampins} (arbitrary units)	-0.12 (0.19)	-0.18 - -0.07
RC_{ampexp} (arbitrary units)	-0.13 (0.20)	-0.19 - -0.07
AB_{ampins} (arbitrary units)	-0.07 (0.16)	-0.12 - -0.02
AB_{ampexp} (arbitrary units)	-0.07 (0.16)	-0.12 - -0.03
RC_{ampins}/AB_{ampins}	-0.09 (0.35)	-0.19 – 0.01
RC_{ampexp}/Ab_{ampexp}	-0.09 (0.34)	-0.19 – 0.00

***μ:** mean value; **sd:** standard deviation; **95%CI:** 95% confidence intervals



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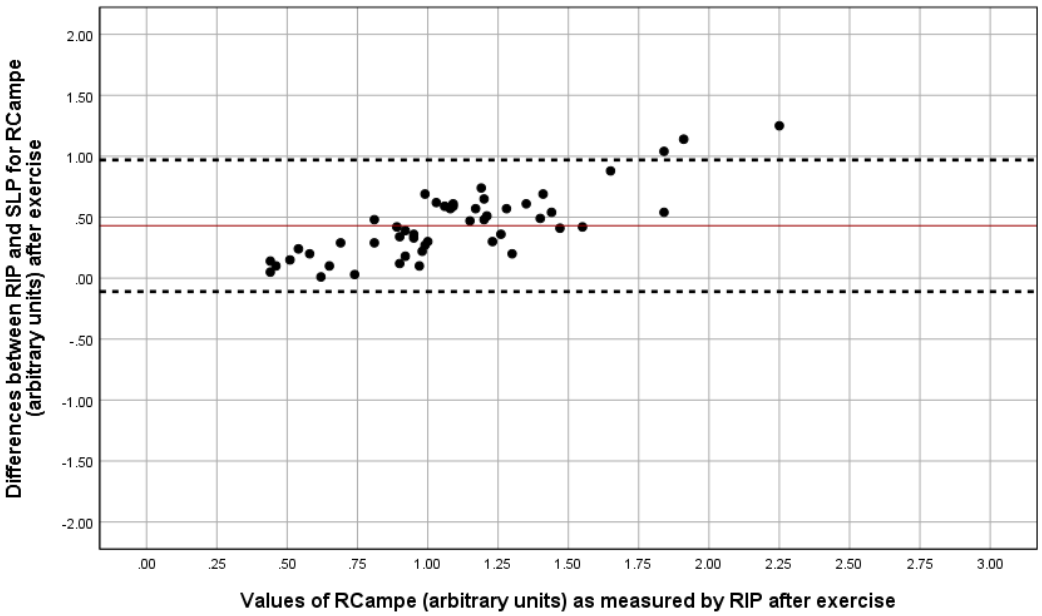
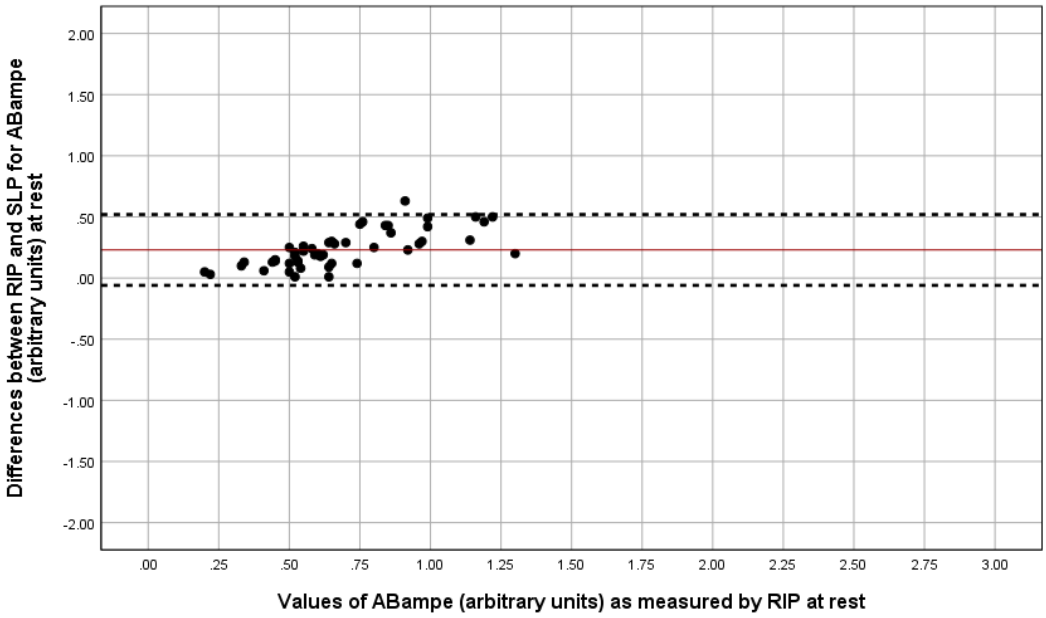


(b)

Figure C1-7: The Bland and Altman plot for the RC_{ampexp} at rest (plot a) and after exercise (plot b)



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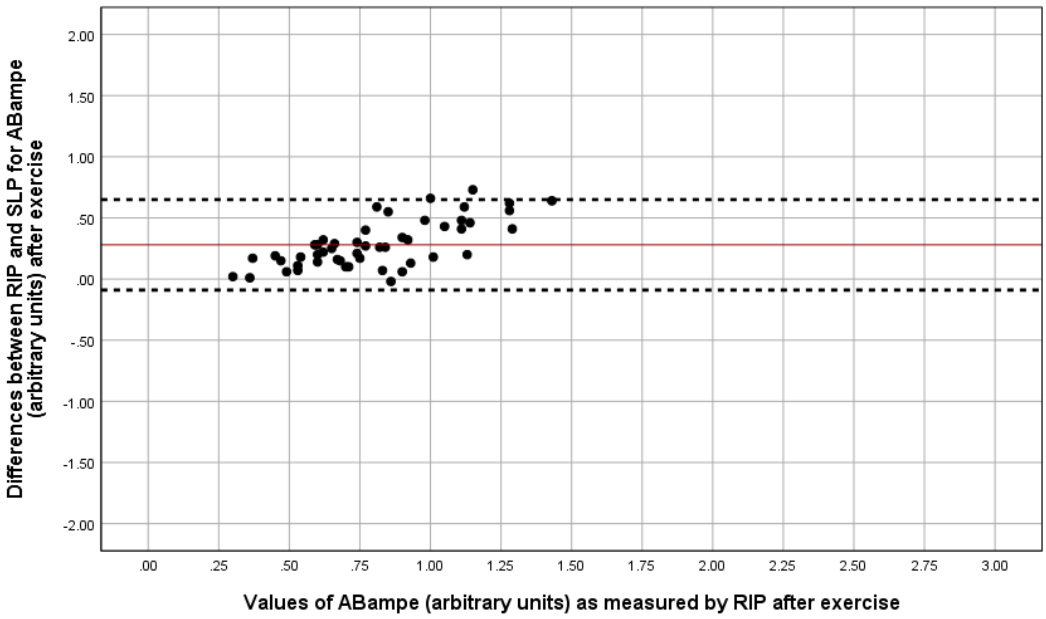
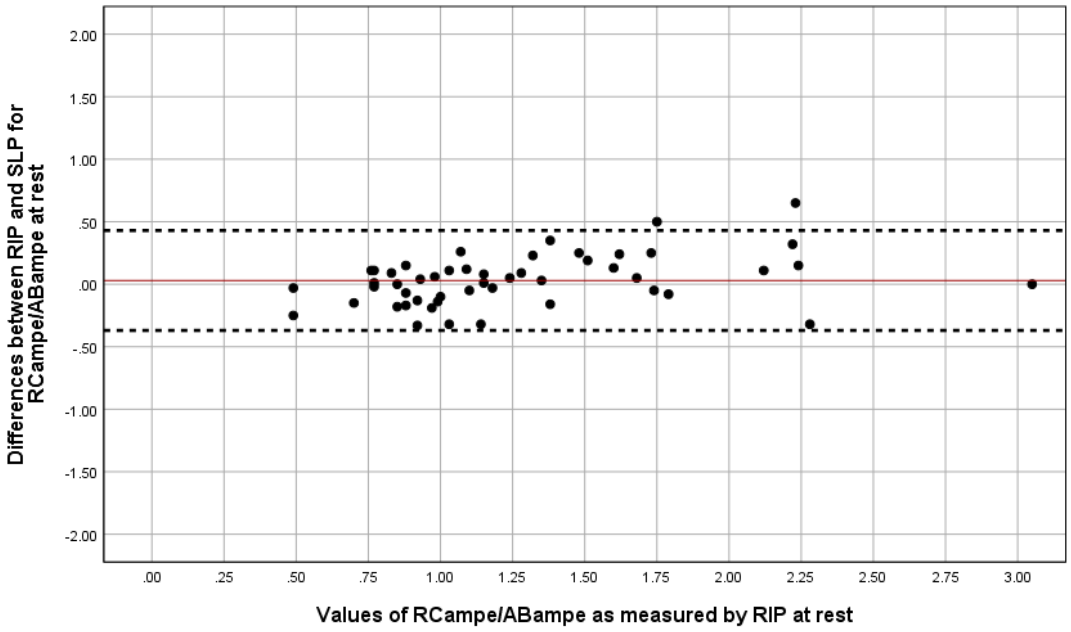


(b)

Figure C1-8: The Bland and Altman plot for the AB_{ampexp} at rest (plot a) and after exercise (plot b)



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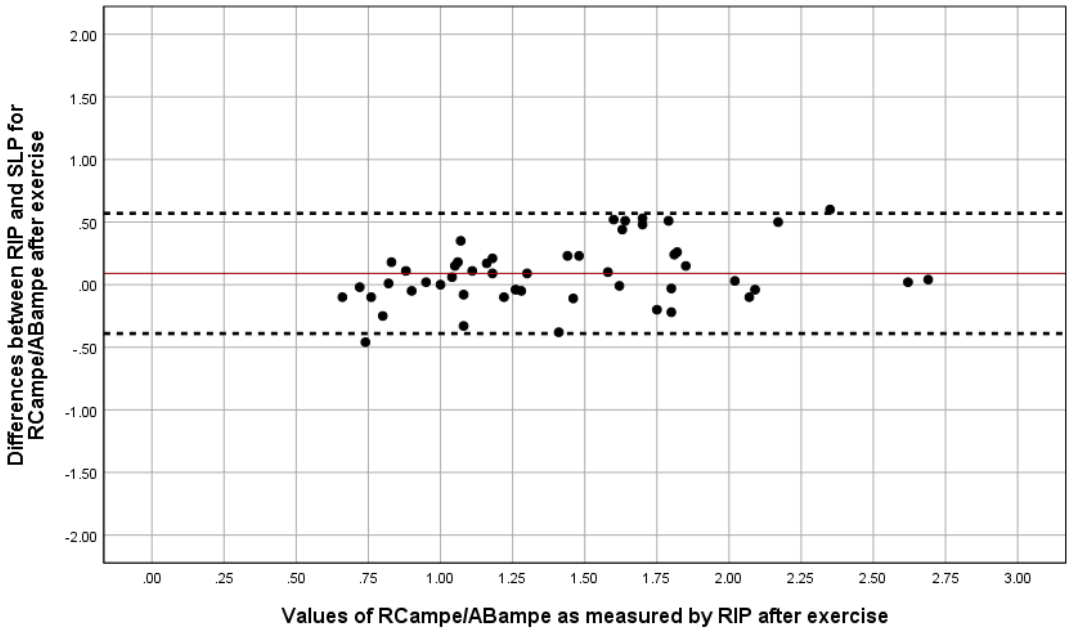


(b)

Figure C1-9: The Bland and Altman plot for the RC_{ampexp}/AB_{ampexp} at rest (plot a) and after exercise (plot b)

Table C1-11: Mean differences in RC_{ampexp}, AB_{ampexp} and RC_{ampexp}/AB_{ampexp} between the RIP and the SLP after a breath-by-breath analysis (no of breath cycles: 7690)

Breathing parameter	**μ* (sd)**	**˜95% CI* Lower-upper bound**	**&95%LOA* Lower- upper limit**
RC_{ampexp} (arbitrary units)	0.43 (0.32)	0.42 – 0.43	-0.19 – 1.05
AB_{ampexp} (arbitrary units)	0.28 (0.21)	0.28 – 0.29	-0.13 – 0.69
RC_{ampexp}/AB_{ampexp}	(0.12) (0.68)	0.10 – 0.13	-1.33 – 1.45

* **μ:** mean value; **sd:** standard deviation; **95%CI:** 95% Confidence intervals; **95%LOA:** 95% Limits of agreement

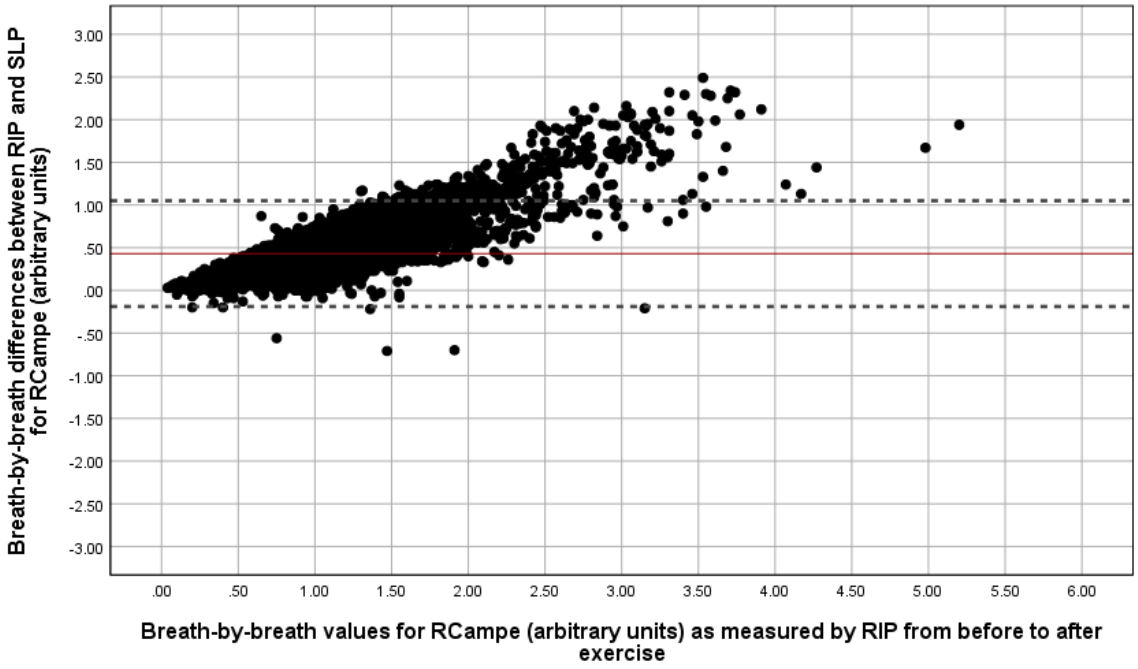


Figure C1-10: The breath-by-breath agreement between the RIP and the SLP for the RC_{ampexp}

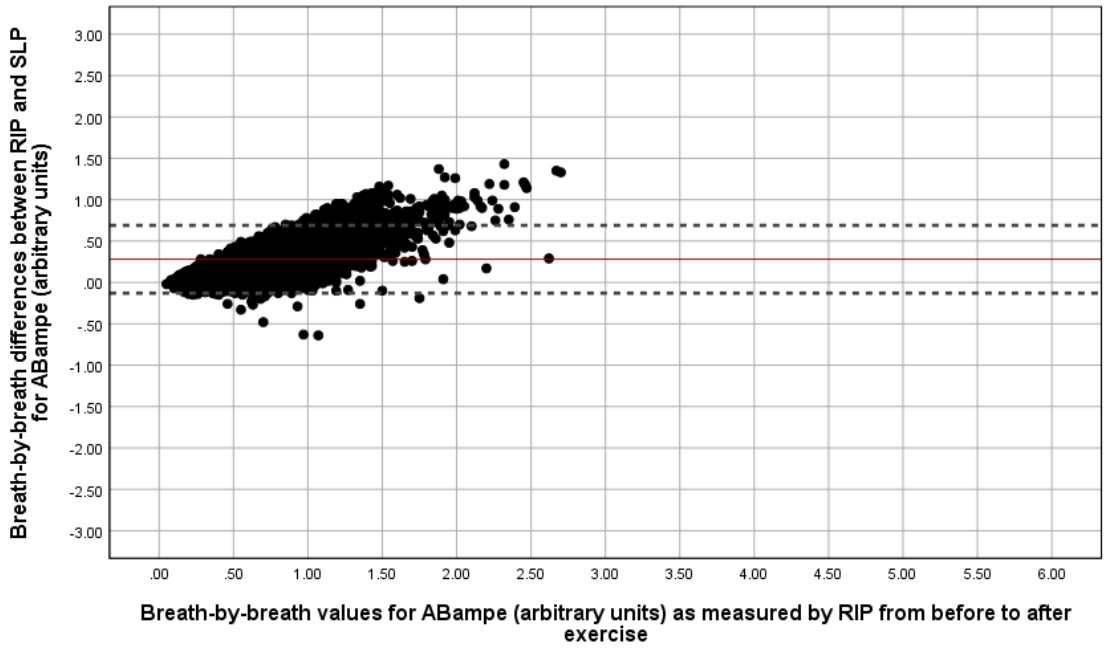


Figure C1-11: The breath-by-breath agreement between the RIP and the SLP for the AB_{ampexp}

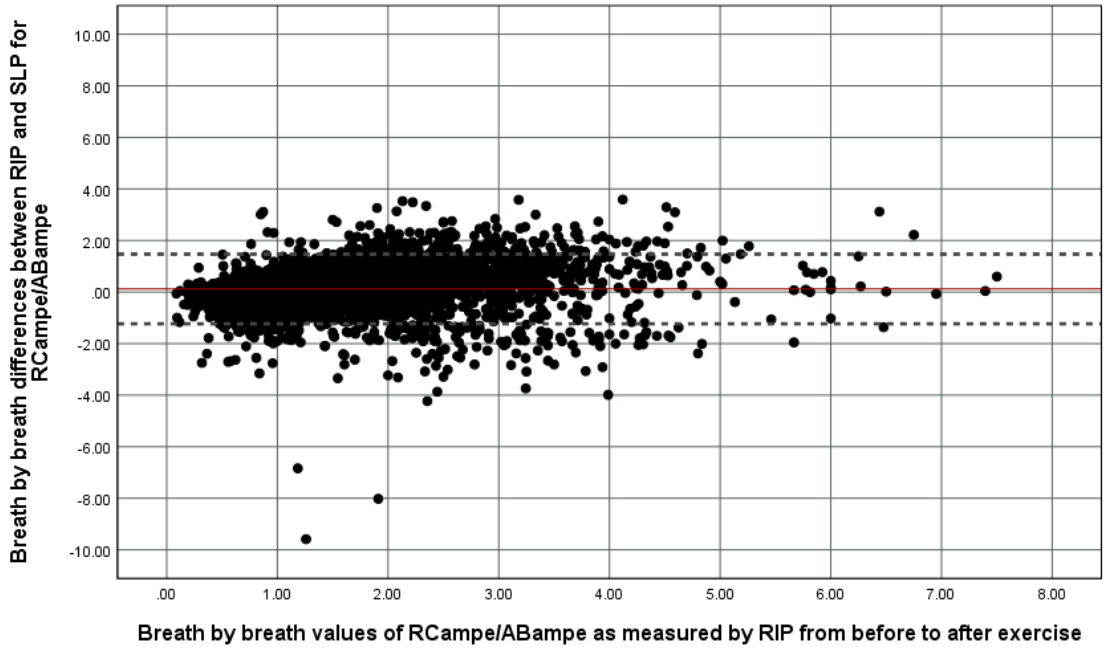


Figure C1-12: The breath-by-breath agreement between the RIP and the SLP for the RC_{ampexp}/AB_{ampexp}

Table C1-12: Mean differences between the RIP and the SLP for the changes in RC_{ampexp}, AB_{ampexp} and RC_{ampexp}/AB_{ampins} after exercise in a sample of 50 adults

Breathing parameter	**μ*** **(sd)**	**95%CI*** **Lower-Upper bound**	**95%LOA*** **Lower-upper limit**
RC_{ampexp} (arbitrary units)	-0.12 (0.22)	-0.19 - -0.06	-0.54 – 0.30
AB_{ampexp} (arbitrary units)	-0.05 (0.15)	-0.09 – 0.00	-0.36 – 0.26
RC_{ampexp}/AB_{amexp}	-0.06 (0.21)	-0.12 – 0.01	-0.49 – 0.37

* **μ:** mean value; **sd:** standard deviation; **95%CI:** 95% Confidence intervals; **95%LOA:** 95% Limits of agreement

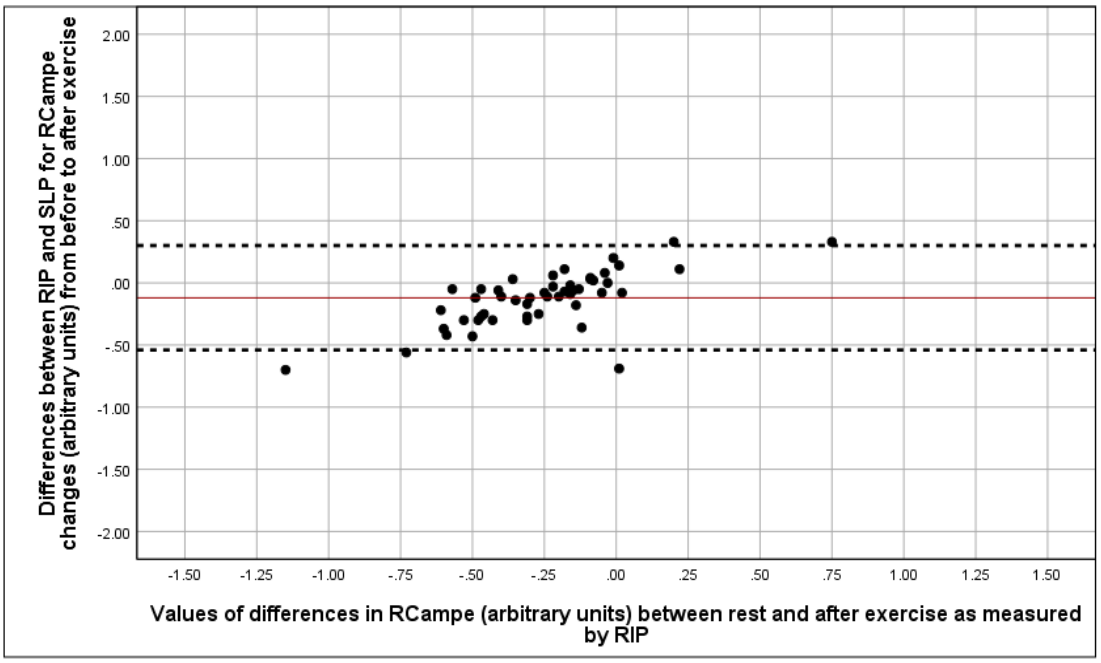


Figure C1-13: The agreement between the RIP and the SLP for the changes in RC_{ampexp} between resting breathing and after exercise

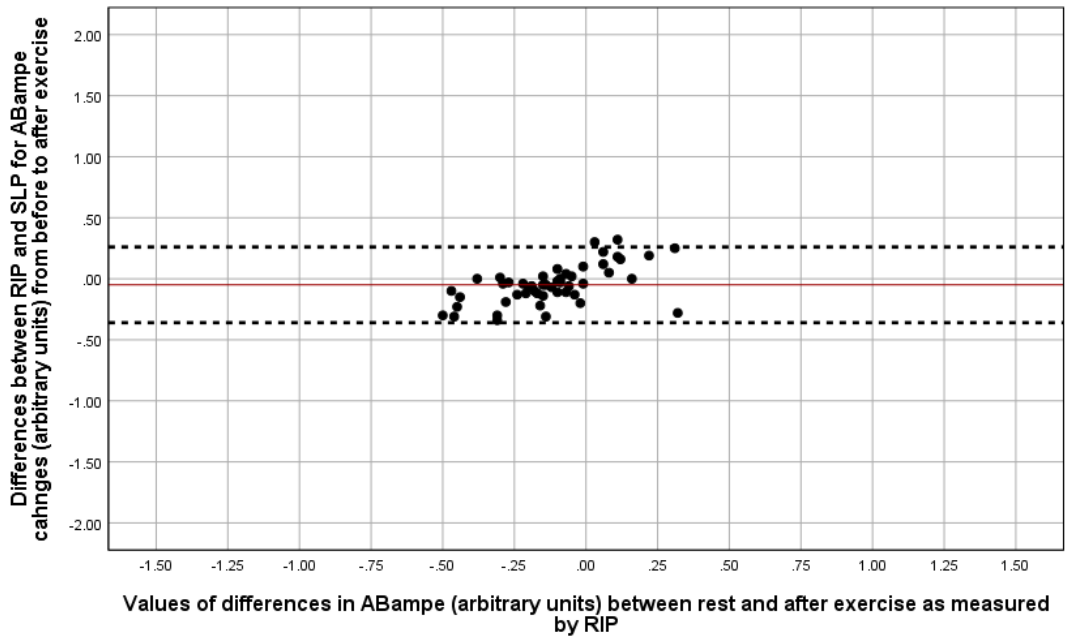


Figure C1-14: The agreement between the RIP and the SLP for the changes in AB_{ampexp} between resting breathing and after exercise

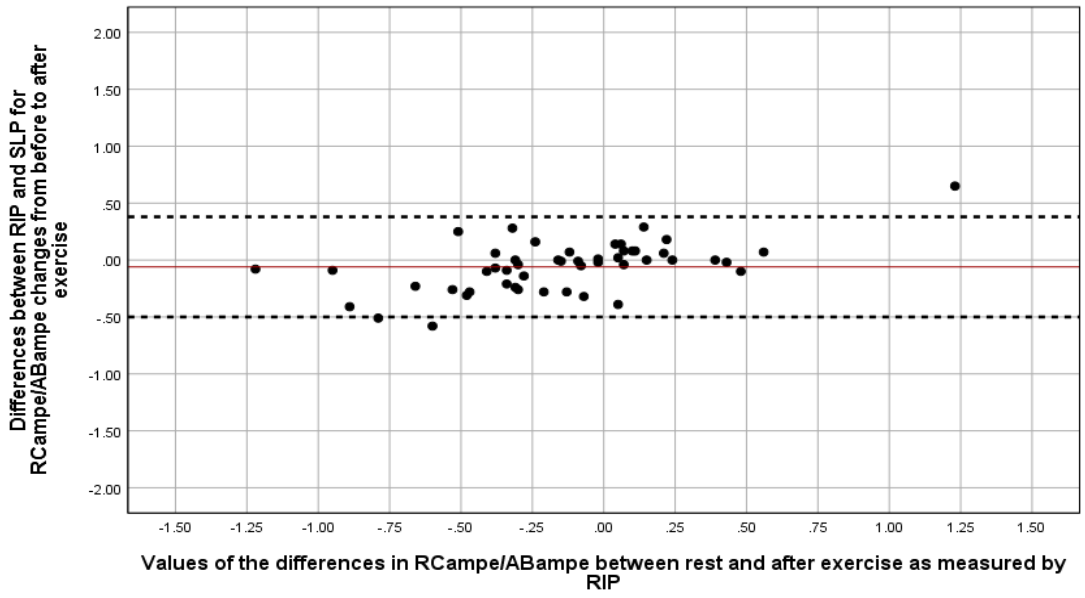


Figure C1-15: The agreement between the RIP and the SLP for the changes in RC_{ampexp}/AB_{ampexp} between resting breathing and after exercise

C.2 Supplemental results of the correlational study

Table C2-1: Deleted breath cycles in 13 asthma patients during breathing pattern data extraction

Participant	No of deleted breath cycles
S2P03	3
S2P11	7
S2P19	1
S2P22	3
S2P26	2
S2P28	4
S2P34	2
S2P48	5
S2P59	1
S2P66	3
S2P83	3
S2P99	4
S2P13	2

Table C2-2: Mean values for both RC_{amp}/AB_{amp} and $\%CoV_{RCamp/ABamp}$ during the expiration phase in the total sample (n=122) of the correlation study

Variable	**μ***	**sd***	**95%CI*** **Lower-upper**	**Min-Max***
RC_{ampexp}/AB_{ampexp}	1.41	0.68	1.28-1.52	0.37-5.31
$\%CoV_{RCampexp/ABampexp}$	20.39	10.07	18.35-21.97	7.05-57.62

* **μ**: mean value; **sd**: standard deviation; **95%CI:** 95% Confidence intervals; **Min-Max:** Minimum and maximum value

Table C2-3: Median values for the RC_{amp}/AB_{amp} and $\%CoV_{RCamp/ABamp}$ during the expiration phase between asthma control groups

	Well-controlled asthma group (n=59)		Not well-controlled asthma group (n=63)	
Variable	**M***	**Min-Max***	**M**	**Min-Max**
RC_{ampexp}/AB_{ampexp}	1.29	0.43-4.20	1.33	0.37-5.31
$\%CoV_{RCampexp/ABampexp}$	14.82	6.05-24.82	26.45	7-74-57.62

***M:** median; **Min-Max**: Minimum and maximum value

Table C2-4: Summary of U-statistics after making comparisons in RC_{amp}/AB_{amp} and $\%CoV_{RCamp/ABamp}$ during the expiration phase between asthma control groups

	Well controlled group(n=59)	Not well controlled group(n=63)		
Variable	**Mean Rank**	**Mean Rank**	**Mann-Whitney U**	**Sig.**
RC_{ampexp}/AB_{ampexp}	60.48	62.45	1798	0.729
$\%CoV_{RCampexp/ABampexp}$	44.31	77.60	844	0.000*

*starred value is a significant result at $p<0.01$ after Bonferroni correction for multiple t-tests

Table C2-5: Tolerance values and variance inflation factor of regression model 1 including the RC_{amp}/AB_{amp} during the expiration phase

Regression Model 1*	Tolerance	VIF*
RR	0.932	1.073
Ti/Te	0.933	1.071
RC_{ampexp}/AB_{ampexp}	0.986	1.012

*Regression model 1 included absolute measurements of the examined breathing components; **VIF:** Variance inflation factor

Table C2-6: Tolerance values and variance inflation factor (VIF) of regression model 2

Model 2a*	**Tolerance**	**VIF***
$\%CoV_{RR}$	0.817	1.224
$\%CoV_{Ti/Te}$	0.717	1.394
$\%CoV_{RCampinsp/ABampinsp}$	0.749	1.335
Model 2b*	**Tolerance**	**VIF**
$\%CoV_{RR}$	0.817	1.224
$\%CoV_{Ti/Te}$	0.717	1.394
$\%CoV_{RCampexp/ABampexp}$	0.748	1.334

*Model 2a includes the coefficient of variation for the respiratory rate, the proportionality of inspiration over expiration phase and the proportionality of ribcage amplitude to abdominal amplitude during the inspiration phase; Model 2b includes the coefficient of variation for the respiratory rate, the proportionality of inspiration over expiration phase and the proportionality of ribcage amplitude to abdominal amplitude during the expiration phase; VIF: variance inflation factor

Table C2-7: Results of multiple binary logistic regression for regression model 1 including RC_{amp}/AB_{amp} during the expiration phase to predict asthma control

		95% CI for Odds Ratio			
Predictors	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig**
RR (bpm)	0.16(0.05)	1.06	1.17	1.30	0.002*
Ti/Te	0.10 (1.79)	0.03	1.10	37.36	0.954
RC_{ampexp}/AB_{ampexp}	0.07(0.29)	0.61	1.07	1.88	0.812

B_0= 0.07, R^2: 0.09, R: 0.12, -2LL:157.38; *starred value was found to be a significant result at p<0.05

Table C2-8: Results of multiple binary logistic regression applying regression model 2 which included the $\%CoV_{RCamp/ABamp}$ during the expiration phase to predict asthma control

		95% CI for Odds Ratio			
Predictors	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig**
$\%CoV_{RR}$(bpm)	0.15 (0.05)	1.05	1.16	1.29	0.000*
$\%CoV_{Ti/Te}$	0.10 (0.03)	1.04	1.11	1.18	0.001*
$\%CoV_{RCampexp/ABampexp}$	0.09 (0.03)	1.02	1.09	1.17	0.005*

B_0= 0.07, R^2: 0.45, R: 0.55, -2LL:97.09. *starred value are significant result at p<0.05

Table C2-9: Results for the assumption of linearity between significant predictors identified in the regression models and asthma control

Variable	B (SE)	Wald	Exp (B)	Sig
LogRR	0.043 (0.01)	9.623	1.04	0.002*
$LogCoV_{RR}$	-0.19 (0.15)	1.638	0.83	0.201
$LogCoV_{Ti/Te}$	-0.05 (0.07)	1.586	0.85	0.444
$LogCoV_{RC/ABinsp}$	-0.37 (0.25)	2.120	1.45	0.145
$LogCoV_{RC/ABexp}$	-0.37 (0.25)	2.099	1.44	0.141

*stared value is a significant result at $p<0.05$ violating the assumption of linearity

Table C2-10: Classification table for regression model 2 including $\%CoV_{RCamp/ABamp}$ during the expiration phase

	Predicted levels of asthma control via the use of the $\%CoV_{RR}$, the $\%CoV_{Ti/Te}$ and the $\%CoV_{RCampexp/ABampexp}$	
Observed levels of asthma control as determined by ACQ scores	*Well controlled asthma*	*Not well controlled asthma*
Well controlled asthma (n=59)	52	7
Not well controlled asthma (n=63)	15	48

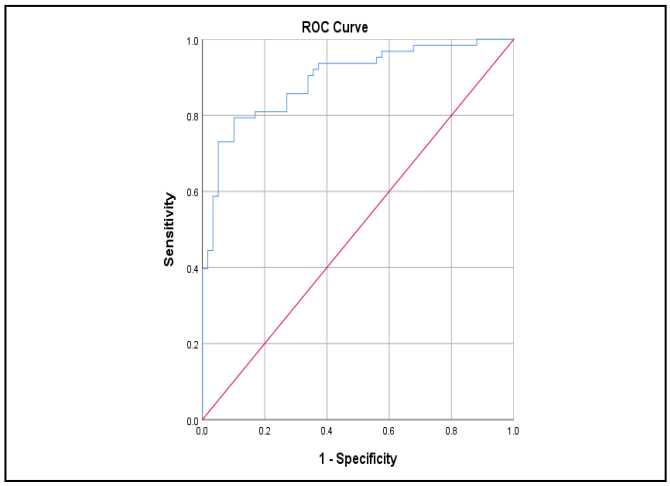


Figure C2-1: The ROC curve of regression model 2 including the $\%CoV_{RCamp/ABamp}$ during the expiration phase

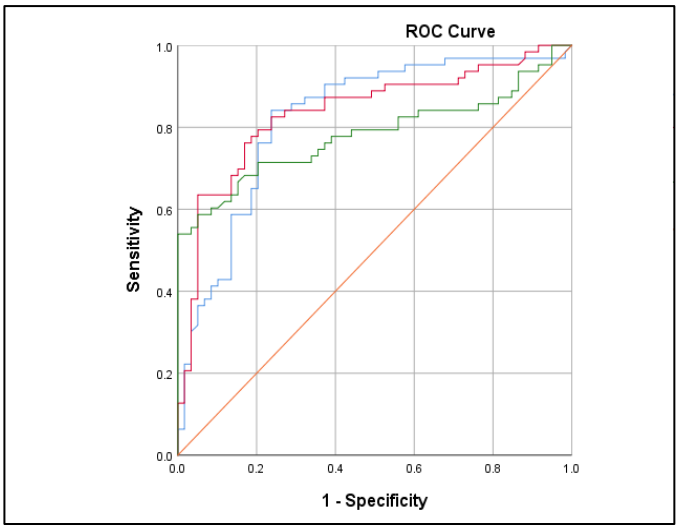


Figure C2-2: The individual ROC curves of the %CoV of the breathing components. Blue, red and green lines are the ROC curve for the $\%CoV_{RR}$, the $\%CoV_{Ti/Te}$, and $\%CoV_{RCampexp/ABampexp}$

Table C2-11: Results regarding the area under the curve (AUC) for $\%CoV_{RCamp/ABamp}$ during the expiration phase used to differentiate between patients with well-controlled and not well-controlled asthma

Breathing component	AUC	Std Error	95%CI Lower-upper	Sig.
$\%CoV_{RCampexp/ABampexp}$	0.773	0.044	0.686-0.859	0.000*

*starred value is a significant result at p<0.05

Table C2-12: Summary of values for the RC_{amp}/AB_{amp} and the $\%CoV_{RCamp/ABamp}$ during the expiration phase between patients with absence and presence of dysfunctional breathing

	Patients with NQ<10 (n=63) NO DB		Patients with NQ≥10 (n=59) Possible DB	
Variable	**M***	**Min-Max**	**M***	**Min-max**
RC/AB_{exp}	1.31	0.43-4.20	1.32	0.37-5.31
$\%CoV_{RC/ABexp}$	14.97	7.05-47.38	21.74	7.74-57.62

*M: median values

Table C2-13: Summary of U-statistics after making comparisons in the RC_{amp}/AB_{amp} and the $\%CoVRC_{amp}/AB_{amp}$ during the expiration phase between the patients with absence and presence of dysfunctional breathing

	Patients with NQ<10 (n=63) NO DB	**Patients with NQ≥10 (n=59) Possible DB**		
Variable	**Mean Rank**	**Mean Rank**	**Mann-Whitney U**	**Sig.**
RC_{ampexp}/AB_{ampexp}	63.06	59.83	1760	0.614
$\%CoV_{RCampexp/ABampexp}$	49.23	74.60	1085	0.000*

*starred value is a significant result at p<0.01 after Bonferroni correction for multiple t-tests

Table C2-14: Regression model 1 including the RC_{amp}/AB_{amp} during the expiration phase used to predict possible presence of dysfunctional breathing

		95% CI for Odds Ratio			
Model 1	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig**
RR (bpm)	0.15 (0.05)	1.05	1.16	1.28	0.004*
Ti/Te	1.92 (1.83)	0.19	6.84	48.20	0.294
RC_{ampexp}/AB_{ampexp}	-0.07 (0.28)	0.54	0.93	1.62	0.802

B0 -0.07, R2: 0.10, R: 0.14, -2LL:155.79. * starred value was found to be a significant result at p<0.05

Table C2-15: Regression model 2 including the $\%CoV_{RCamp/ABamp}$ during the expiration phase used to predict possible presence of dysfunctional breathing

		95% CI for Odds Ratio			
Model 2	**B (SE)**	**Lower**	**Odds Ratio**	**Upper**	**Sig**
$\%CoV_{RR}$	0.08 (0.04)	1.02	1.08	1.16	0.012*
$\%CoV_{Ti/Te}$	0.04 (0.02)	1.01	1.04	1.09	0.022*
$\%CoV_{RCampexp/ABampexp}$	0.05 (0.02)	1.00	1.05	1.10	0.023*

B0 -0.07, R2: 0.25, R: 0.29, -2LL:139.35. Starred values were found to be significant results at p<0.05

Table C2-16: Results for the assumption of linearity between significant predictors identified in the regression models and possible presence of dysfunctional breathing

Variable	B (SE)	Wald	Exp (B)	Sig
LogRR	1.29 (0.42)	9.365	3.622	0.002*
$LogCoV_{RR}$	-0.21 (0.12)	3.059	0.806	0.080
$LogCoV_{Ti/Te}$	-0.27 (0.10)	6.929	0.766	0.072
$LogCoV_{RCampinsp/ABampinsp}$	-0.01 (0.08)	5.428	0.994	0.944
$LogCoV_{RCampexp/ABampexp}$	-0.01 (0.07)	5.428	0.995	0.990

*stared value is a significant result at p<0.05, violating the assumption of linearity

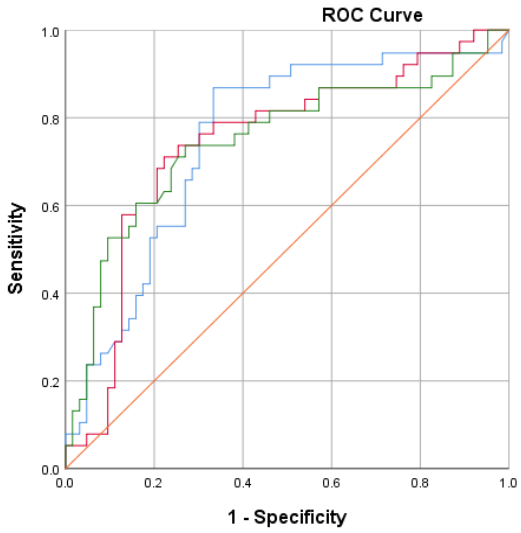


Figure C2-3: Individual ROC curves of the %CoV for breathing components including RC_{amp}/AB_{amp} during the expiration phase in a reduced sample of 101 asthma patients. Blue, red and green lines are the ROC curves for the $\%CoV_{RR}$, the $\%CoV_{Ti/Te}$, and the $\%CoV_{RCampexp/ABampexp}$

Table C2-17: Results regarding the area under the curve (AUC) for $\%CoV_{RCamp/ABamp}$ during the expiration phase, used to differentiate between patients with absence or possible presence of dysfunctional breathing

Breathing component	AUC	Std Error	95%CI Lower-upper	Sig.
$\%CoV_{RCampexp/ABampexp}$	0.749	0.005	0.64-0.85	0.000*

*starred value was considered significant at p<0.05

Table C2-18: Summary of collinearity statistics for regression model 1 and 2 used to predict lung function measurements

Model 1*	**Tolerance**	**VIF**
RR (bpm)	931	1.074
Ti/Te	934	1.071
$RC_{ampinsp}/AB_{ampinsp}$	987	1.013
RC_{ampexp}/AB_{ampexp}	986	1.012
Model 2*	**Tolerance**	**VIF**
$\%CoV_{RR}$	0.821	1.218
$\%CoV_{Ti/Te}$	0.735	1.360
$\%CoV_{RCampinsp/ABampins}$	0.779	1.283
$\%CoV_{RCampexp/ABampexp}$	0.788	1.281

*__Model 1__ includes the absolute measurements of the respiratory rate, the proportionality of inspiration phase to expiration phase and the proportionality of ribcage amplitude to abdominal amplitude during the inspiration phase or the expiration phase; __Model 2__ includes the variation of the respiratory rate, the proportionality of inspiration phase to expiration phase and the proportionality of ribcage amplitude to abdominal amplitude during the inspiration phase or the expiration phase

Table C2-19: Regression model 1 including RC_{amp}/AB_{amp} during the expiration phase used to predict the $\%FEV_{1predicted}$

	Unstandardized Coefficients	**Standardised Coefficients**	**95%CI for B**		
Model 1	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-1.55 (0.54)	-0.259	-2.63	-0.48	0.005*
Ti/Te	33.13 (20.57)	0.146	-7.60	43.86	0.110
RC_{ampexp}/AB_{ampexp}	5.30 (3.30)	0.144	-1.14	11.63	0.104

Bo 81.90, R^2 0.10, Adjusted R^2 0.07, F-ratio -4.306 (Sig 0.006); stared value is a significant result at $p<0.05$

Table C2-20: Regression model 2 including the %CoV of RC_{amp}/AB_{amp} during the expiration phase used to predict the $\%FEV_{1predicted}$

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Model 2	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-0.47 (0.39)	-0.11	-1.25	-0.31	0.231
$\%CoV_{Ti/Te}$	-0.56 (0.23)	-0.25	-1.02	-0.11	0.015*
$\%CoV_{RCampexp/ABampexp}$	-0.07 (0.25)	-0.02	-0.53	0.45	0.782

B_0 82.29, R^2 0.11, Adjusted R^2 0.09, F-ratio 4.943 (Sig 0.003); *starred value is a significant result at p<0.05

Table C2-21: Regression model 1 including the RC_{amp}/AB_{amp} during the expiration phase used to predict FEV_1/FVC

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Model 1	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-0.39 (0.293)	-0.12	-0.97	0.19	0.189
Ti/Te	2.37 (11.11)	0.02	-19.62	14.37	0.831
RC_{ampexp}/AB_{ampexp}	3.00 (1.78)	0.15	-0.53	6.55	0.092

B_0 78.10 , R^2 0.09, R 0.201, Adjusted R^2 0.02, F-ratio 1.695 (Sig 0.181)

Table C2-22: Regression model 2 including the %CoV of RC_{amp}/AB_{amp} during the expiration phase used to predict the FEV_1/FVC

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Model 2	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-0.23 (0.21)	-0.11	-0.66	-0.19	0.277
$\%CoV_{Ti/Te}$	-0.13 (0.12)	-0.12	-0.38	0.11	0.284
$\%CoV_{RCampexp/ABampexp}$	-0.04 (0.12)	-0.01	-0.28	0.26	0.954

B_0 83.99, R^2 0.04. R 0.19, Adjusted R^2 0.01, F-ratio 1.470 (Sig 0.226)

Table C2-23: Regression model 1 including the RC_{amp}/AB_{amp} during the expiration phase used to predict the PEF

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Model 1	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-7.64 (3.54)	-0.20	-14.67	-0.621	0.033*
Ti/Te	137.96 (134.42)	0.10	-128.22	404.16	0.307
RC_{ampexp}/AB_{ampexp}	-3.46 (21.57)	-0.01	-45.18	39.24	0.809

B_0 493.34, R^2 0.04, Adjusted R^2 0.02, F-ratio 1.631 (Sig 0.186); *starred value is a significant result at $p<0.05$

Table C2-24: Regression model 2 including the %CoV of RC_{amp}/AB_{amp} during the expiration phase used to predict the PEF

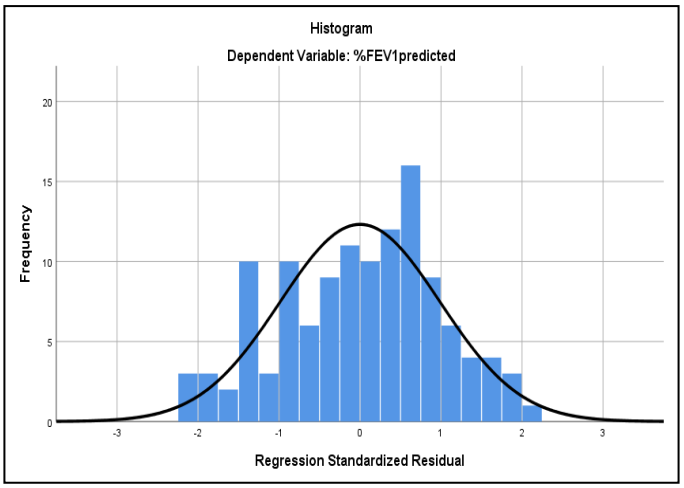
	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Model 2	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-2.15 (2.50)	-0.08	-7.11	-0.81	0.392
%CoVTi/Te	-4.02 (1.45)	-0.29	-6.89	-1.16	0.006*
$\%CoV_{RCampexp/ABampexp}$	-0.03 (1.57)	0.01	-2.88	3.34	0.982

B_0 594.15, R^2 0.11, Adjusted R^2 0.09, F-ratio 4.744 (Sig 0.004); *starred value is a significant result at $p<0.05$

Table C2-23: Assessment of the assumption of independent errors for regression models used to predict lung function measurements

	$\%FEV_{1predicted}$	FEV_1/FVC	PEF (l/m)
Regression Model	**Durbin-Watson***	**Durbin-Watson**	**Durbin-Watson**
RR, Ti/Te, $RC_{ampinsp}/AB_{ampinsp}$	1.145	1.651	1.735
RR, Ti/Te, RC_{ampexp}/AB_{ampexp}	1.145	1.652	1.736
$\%CoV_{RR}$, $\%CoV_{Ti/Te}$, $\%CoV_{RCampinsp/ABampinsp}$	1.241	1.733	1.751
$\%CoV_{RR}$, $\%CoV_{Ti/Te}$, $\%CoV_{RCampexp/ABampexp}$	1.236	1.732	1.748

*tests for correlations between adjacent residuals; a value <2 indicates a positive correlation with values <1 or >3 being cause of concern



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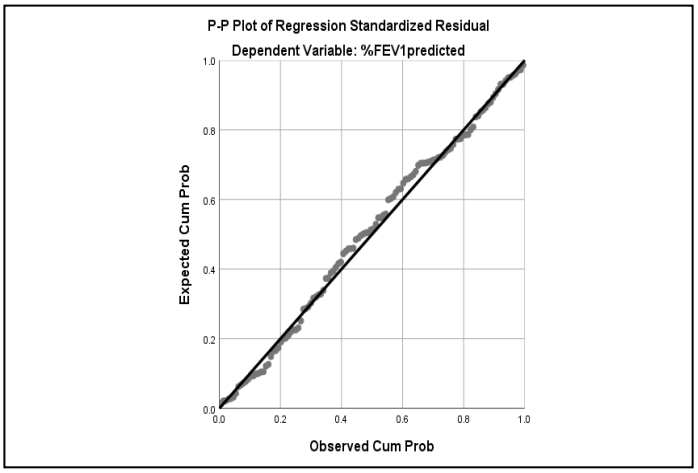

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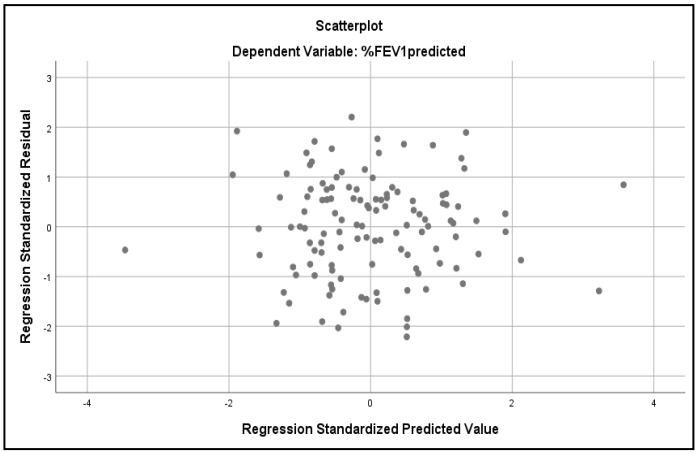
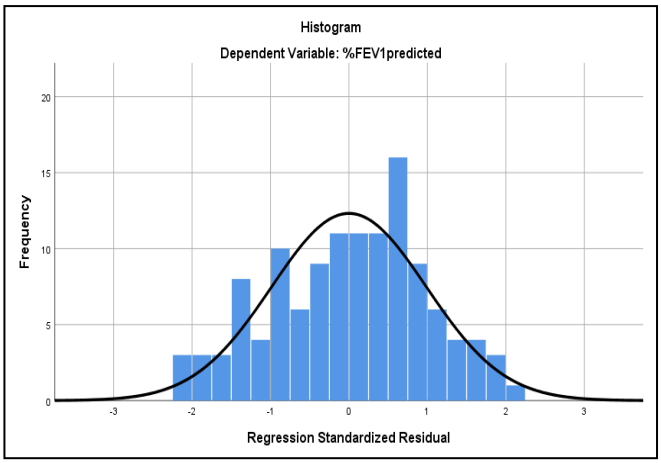


(C)

Figure C2-4: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (c), including the RR, the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp,}$ used to predict the $\%FEV_{1predicted}$



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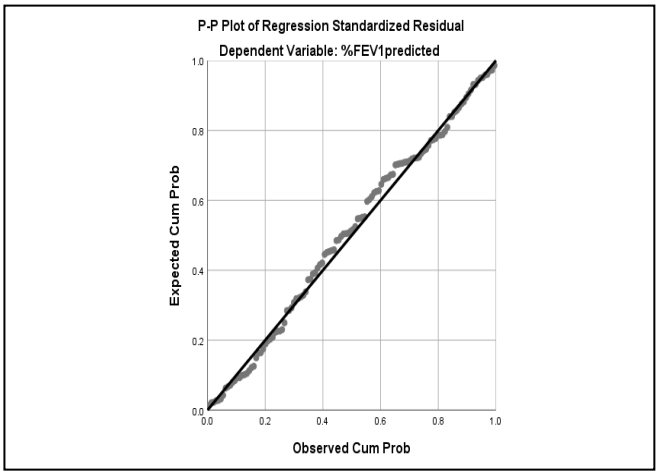

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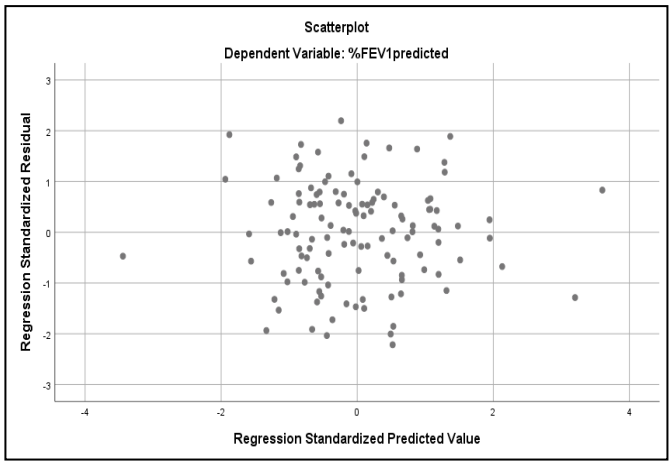
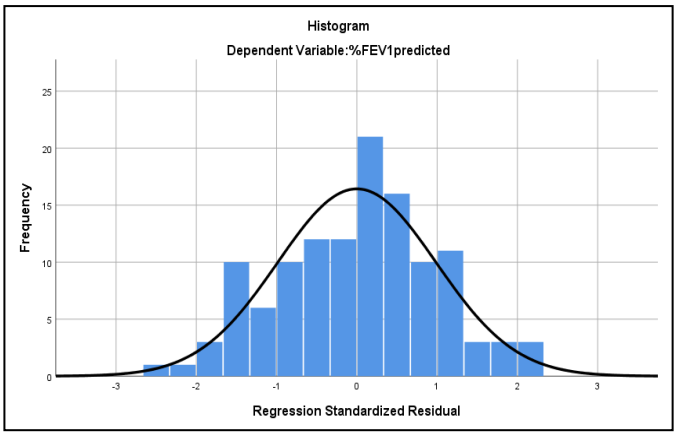


(c)

Figure C2-5: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (c), including the RR, the Ti/Te and the RC_{ampexp}/AB_{ampexp}, used to predict the $\%FEV_{1predicted}$



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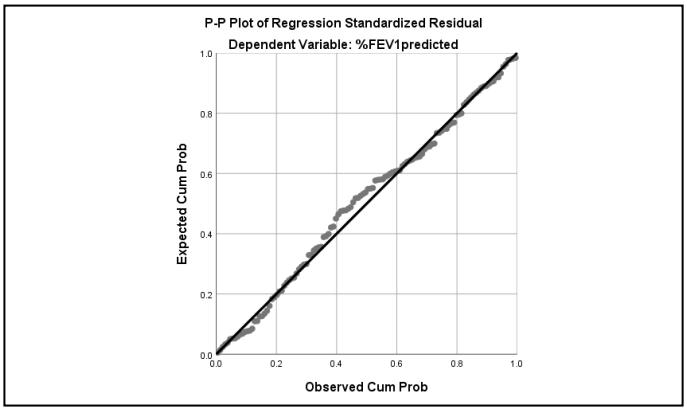

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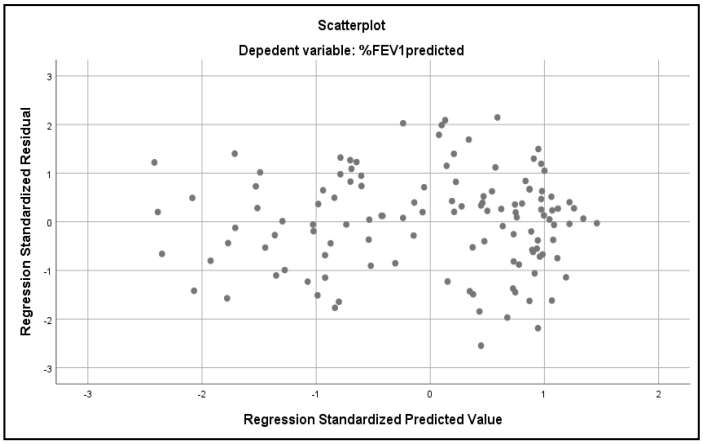
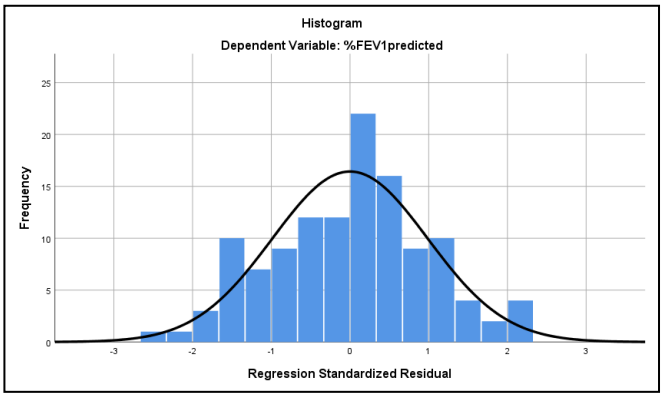


(c)

Figure C2-6: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 (C), including the %CoV of the RR, the Ti/Te and the $RC_{ampsinp}/AB_{ampinsp}$, used to predict the $\%FEV_{1predicted}$



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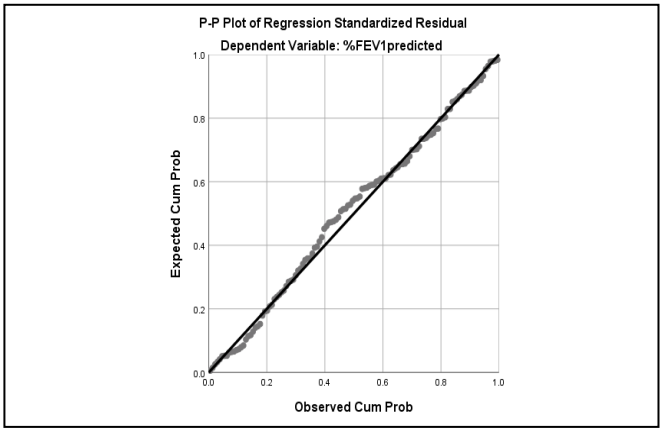

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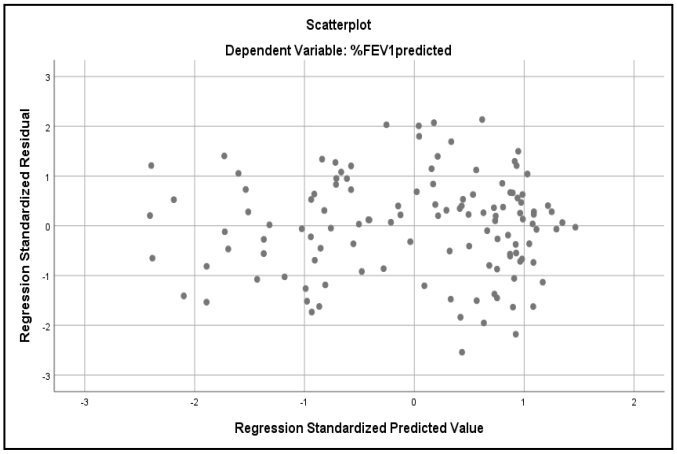

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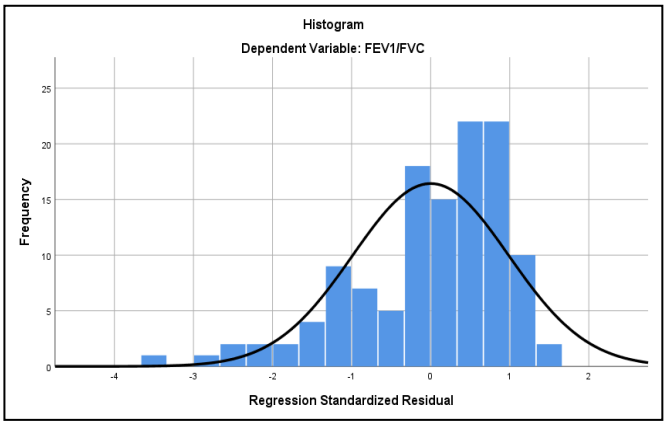
Figure C2-7: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 including the %CoV of the RR, the Ti/Te and the RC_{ampexp}/AB_{ampexp}, used to predict the $\%FEV_{1predicted}$



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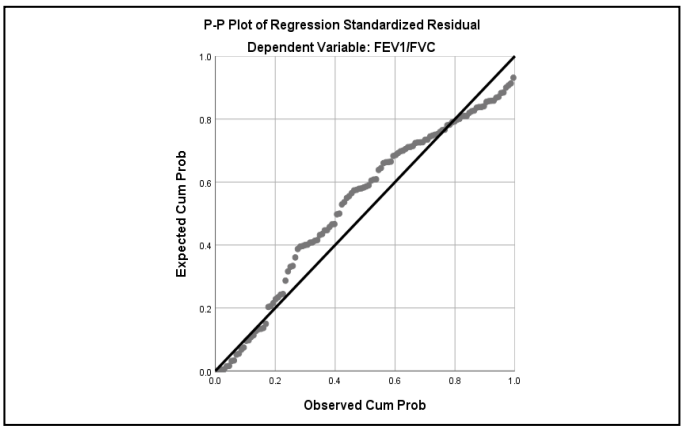

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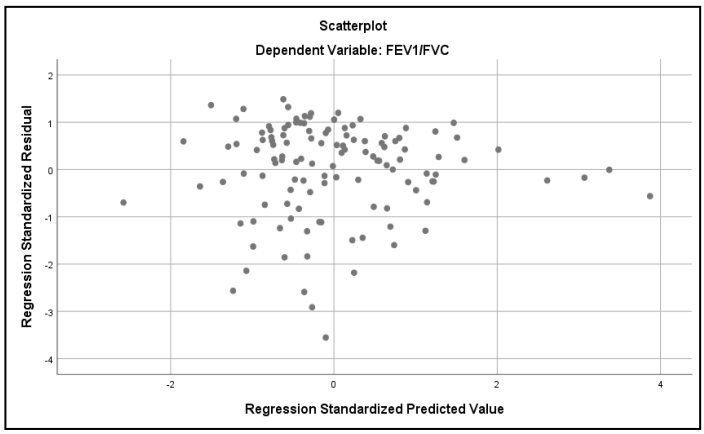

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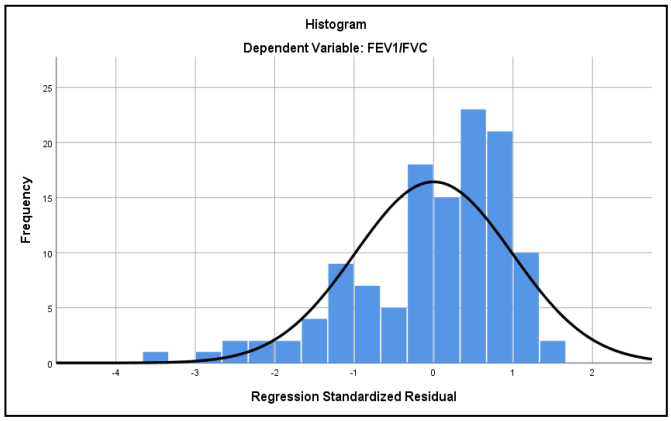
Figure C2-8: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (C), including the RR, the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp}$, used to predict the FEV_1/FVC



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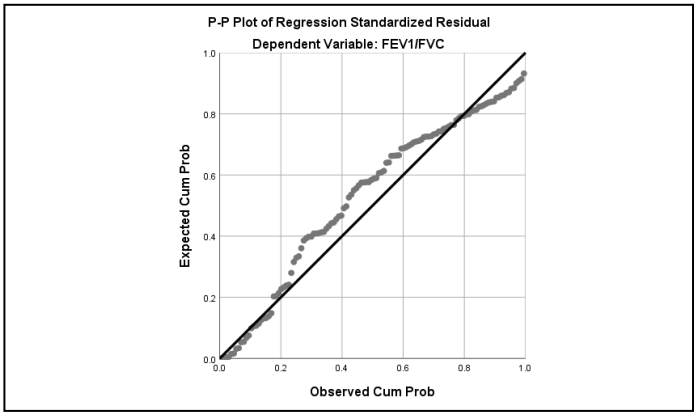

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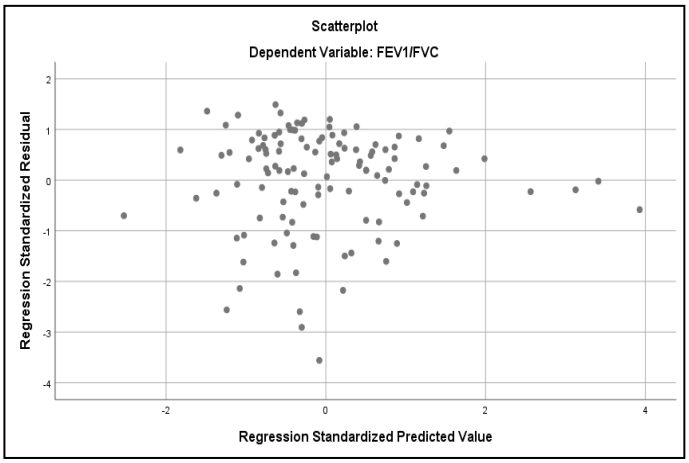

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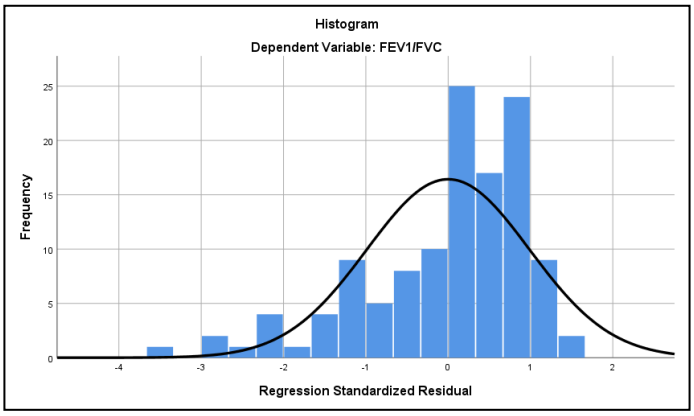
Figure C2-9: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (C), including the RR, the Ti/Te and the $RC_{ampexp}/_{ABampexp}$, used to predict the FEV_1/FVC



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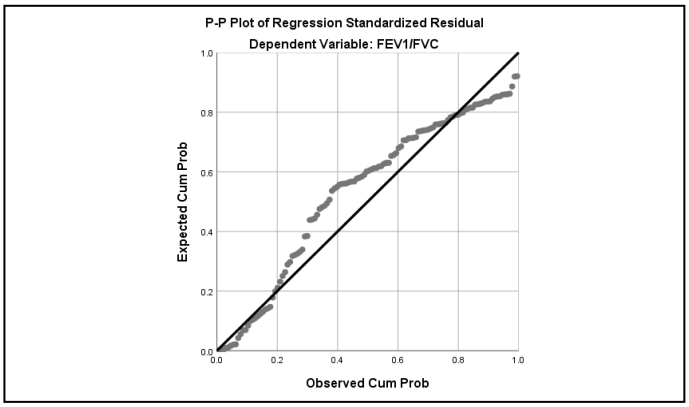

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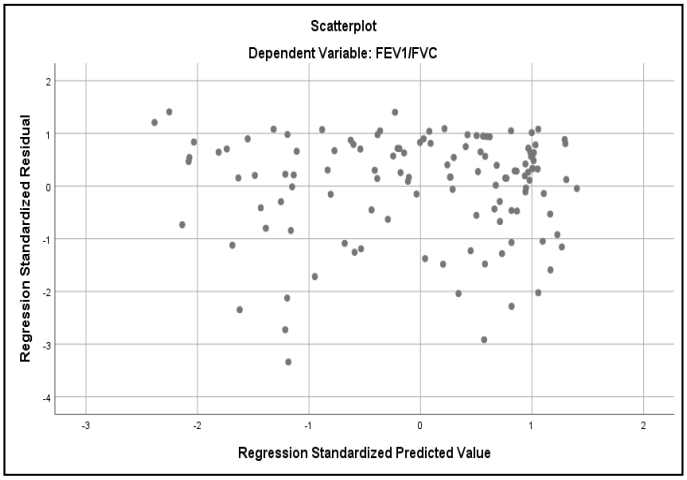

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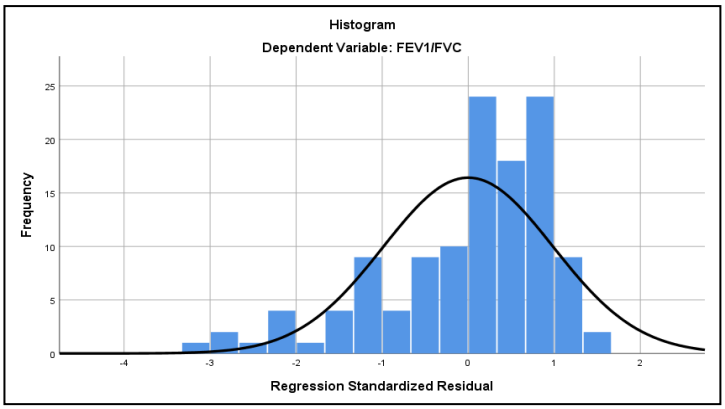
Figure C2-10: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 (C), including the %CoV of the RR, the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp}$, used to predict the FEV_1/FVC



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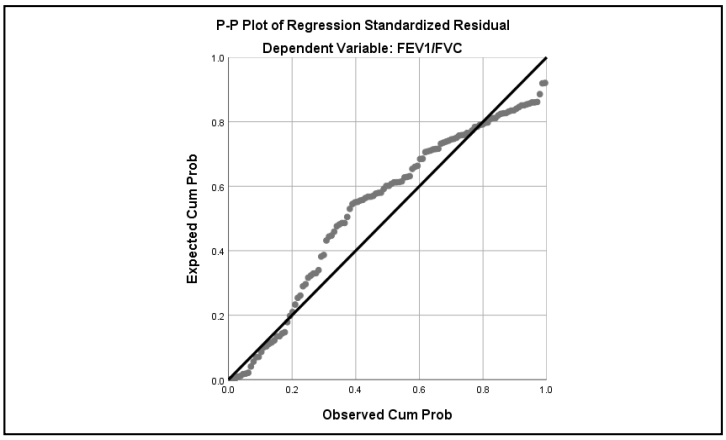

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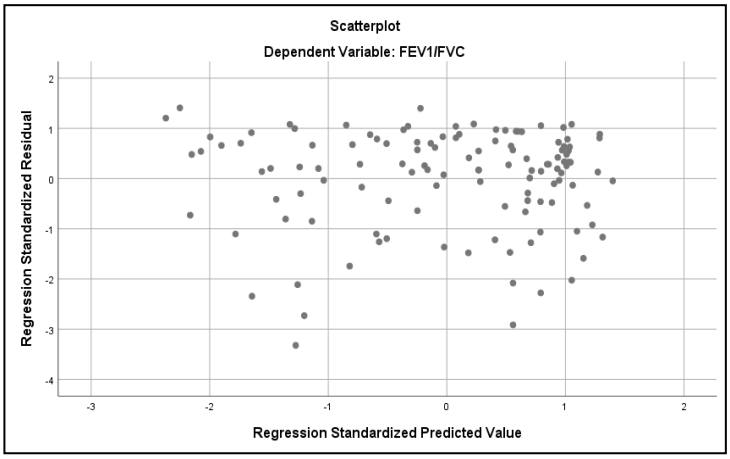

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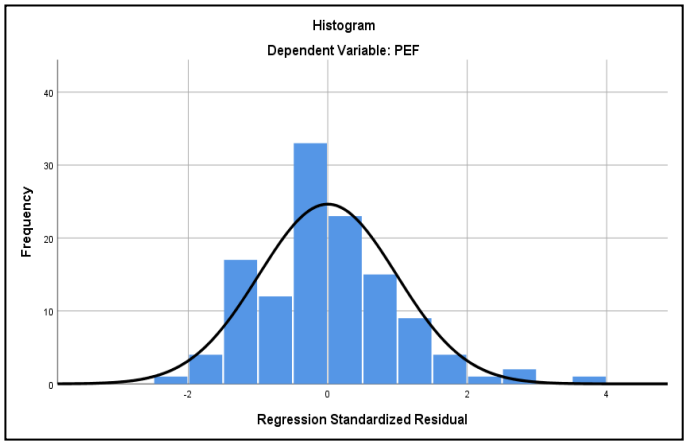
Figure C2-10: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 (C), including the %CoV of the RR, the Ti/Te and the RC_{ampexp}/AB_{ampexp}, used to predict the FEV_1/FVC



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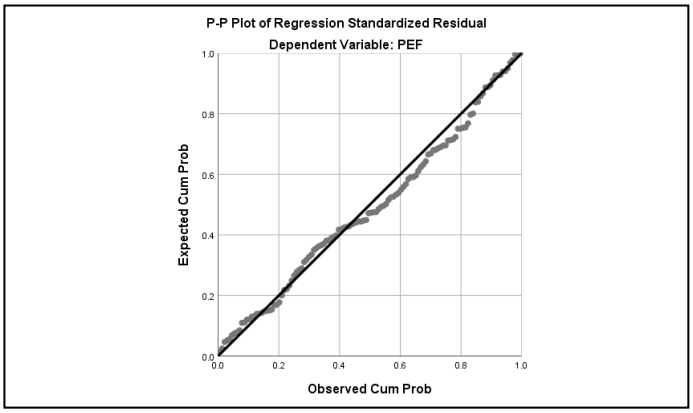

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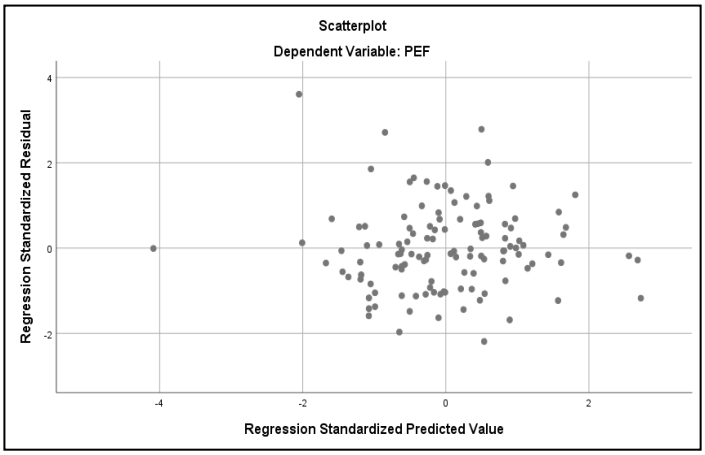

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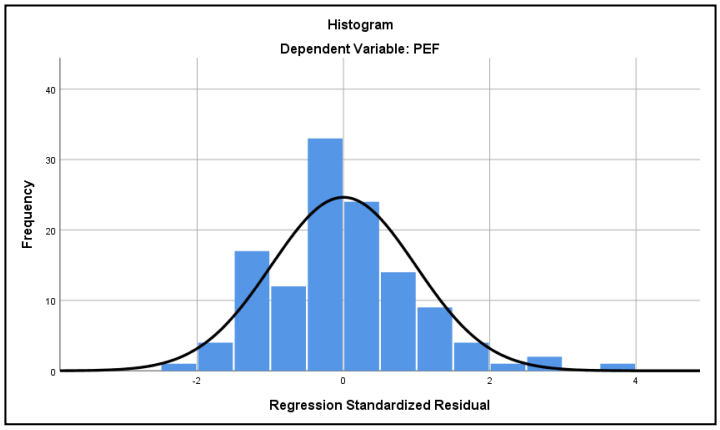
Figure C2-11: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (C), including the RR, the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp}$, used to predict the PEF



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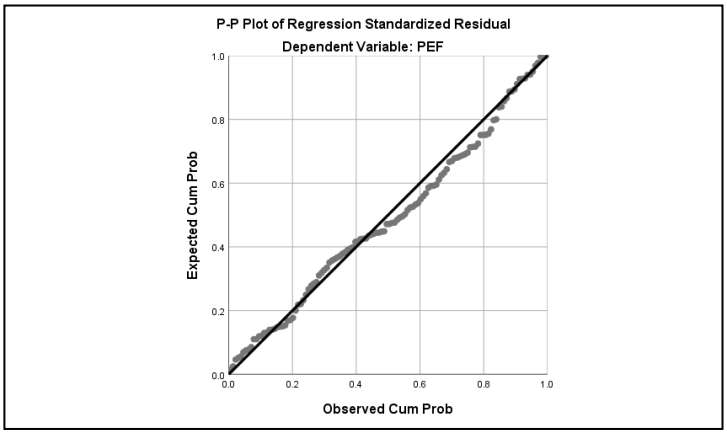

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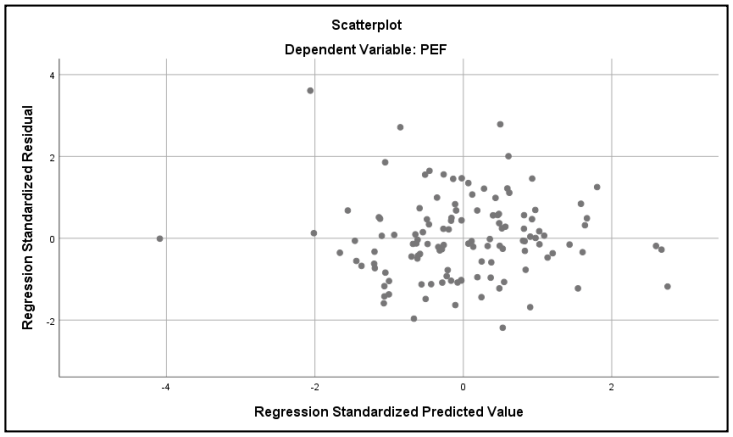

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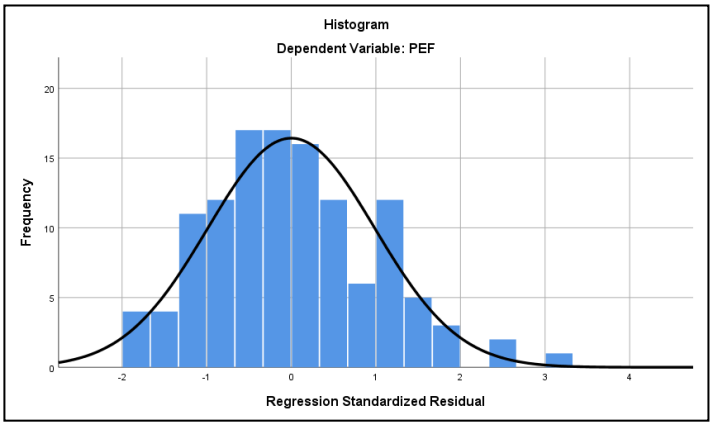
Figure C2-11: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (C), including the RR, the Ti/Te and the RC_{ampexp}/AB_{ampexp}, used to predict the PEF



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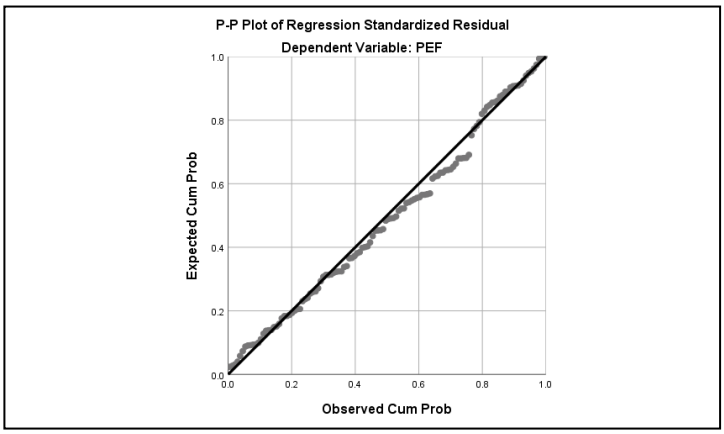

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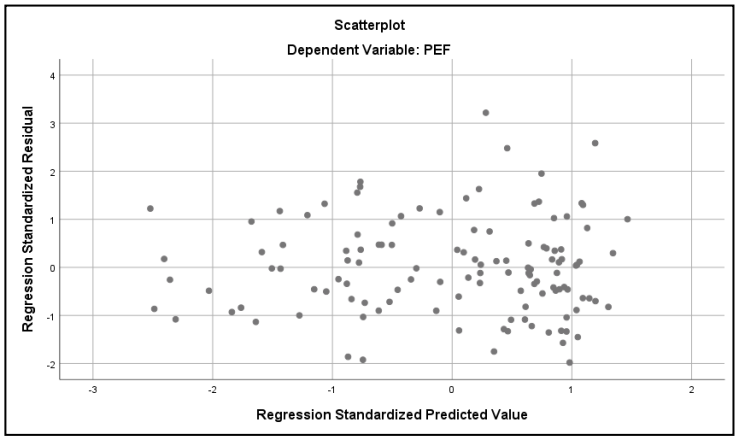

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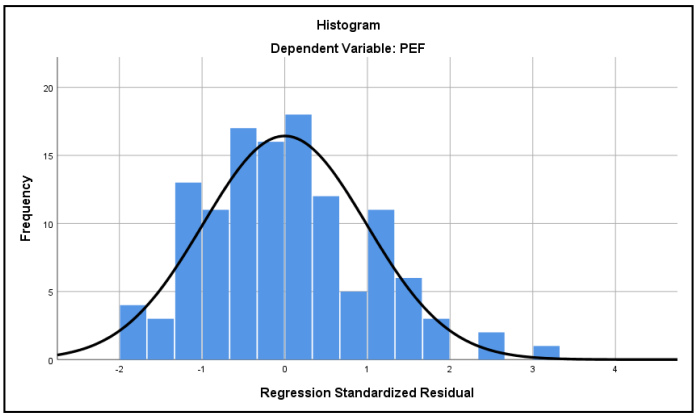
Figure C2-12: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 (C), including the %CoV of the RR, the Ti/Te and the $RC_{ampeinsp}/AB_{ampinsp}$, used to predict the PEF



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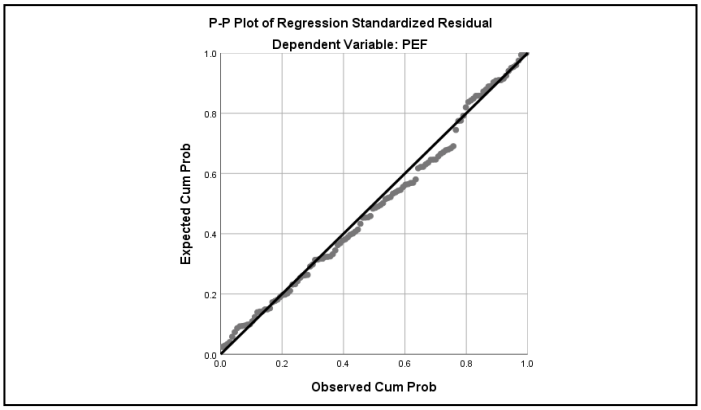

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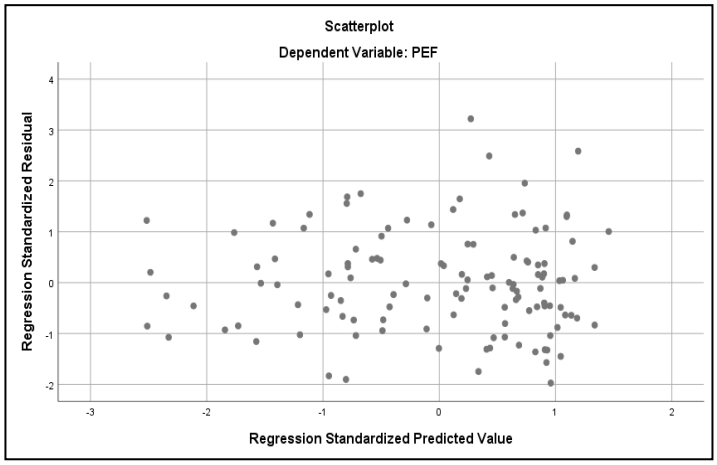


(c)

Figure C2-13: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 (C), including %CoV of the RR, the Ti/Te and the RC_{ampexp}/AB_{ampexp}, used to predict the PEF

Table C2-24: Regression results after using regression model 1, including the RR, the Ti/Te and the RC_{amp}/AB_{amp} during the expiration phase to predict asthma-related quality of life scores

	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Model 1	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
RR (bpm)	-0.07 (0.03)	-0.21	-0.13	-0.01	0.022*
Ti/Te	-0.81 (1.18)	-0.06	-3.15	1.52	0.491
RC_{ampexp}/AB_{ampexp}	-0.20 (0.19)	-0.09	-0.54	0.19	0.303

B_0 7.20, R^2 0.06, R 0.25, adjusted R^2 0.04, F-ratio 2.587 (Sig 0.049); *stared value is a significant result at $p<0.05$

Table C2-25: Regression results after using regression model 2, including the %CoV of the RR, the Ti/Te and the RC_{amp}/AB_{amp} during the expiration phase to predict asthma-related quality of life scores

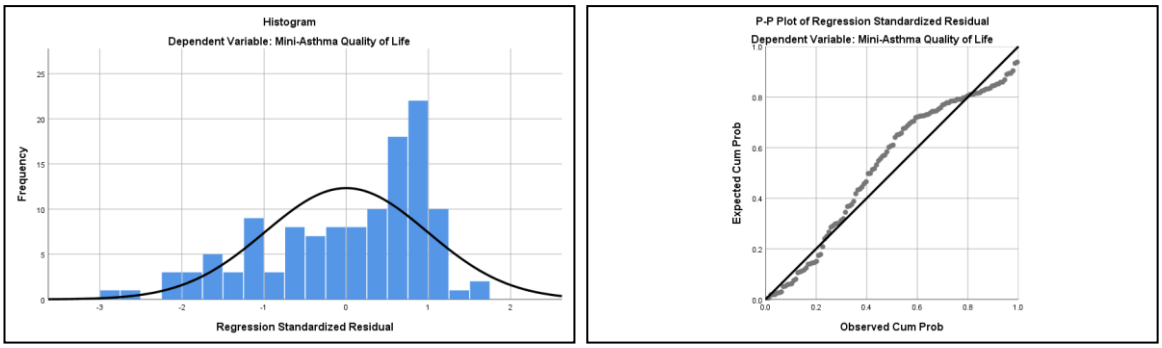
	Unstandardized Coefficients	Standardised Coefficients	95%CI for B		
Model 2	**B (SE)**	**Beta**	**Lower**	**Upper**	**Sig**
$\%CoV_{RR}$	-0.08 (0.02)	-0.34	-0.12	-0.04	0.000*
$\%CoV_{Ti/Te}$	-0.03 (0.01)	-0.22	-0.05	-0.02	0.020*
$\%CoV_{RCampexp/ABampexp}$	-0.02 (0.01)	-0.11	-0.04	-0.01	0.031*

B_0 7.06, R^2 0.27, Adjusted R^2 0.25, F-ratio 14.344 (Sig 0.000); *starred values are significant results at $p<0.05$

Table C2-26: Assessment of the assumption of independent errors for regression models used to predict asthma-related quality of life scores

Regression Model	Durbin-Watson*
RR, Ti/Te, $RC_{ampinsp}/AB_{ampinsp}$	1.164
RR, Ti/Te, RC_{ampexp}/AB_{ampexp}	1.165
$\%CoV_{RR}$, $\%CoV_{Ti/Te}$, $\%CoV_{RCampinsp/ABampinsp}$	1.753
$\%CoV_{RR}$, $\%CoV_{Ti/Te}$, $\%CoV_{RCampexp/ABampexp}$	1.772

*tests for correlations between adjacent residuals; a value <2 indicates a positive correlation with values <1 or >3 being cause of concern



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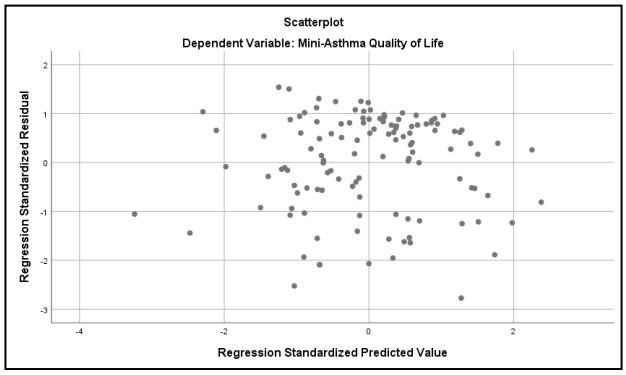

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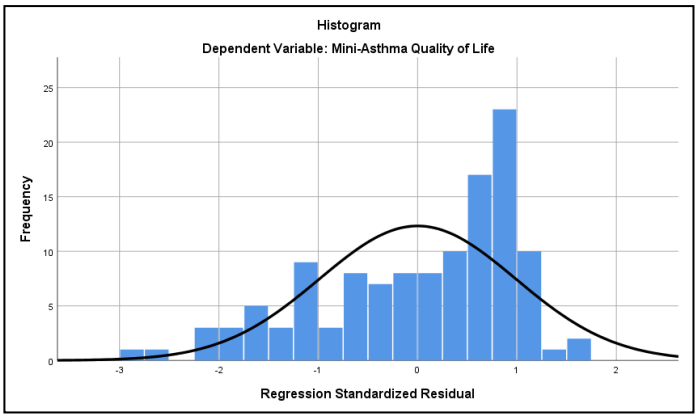
Figure C2-14: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (C), including the RR, the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp}$, used to predict asthma-related quality of life scores



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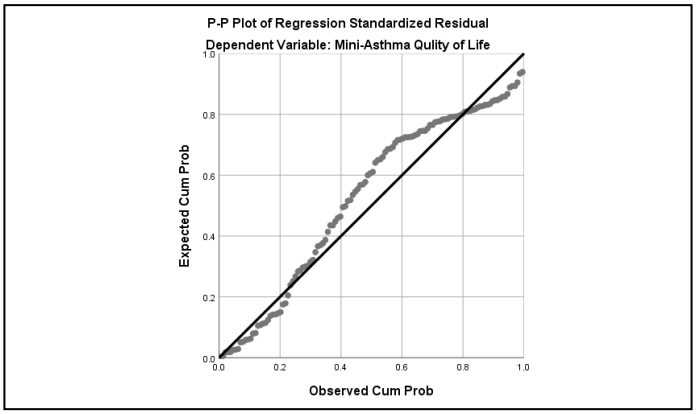

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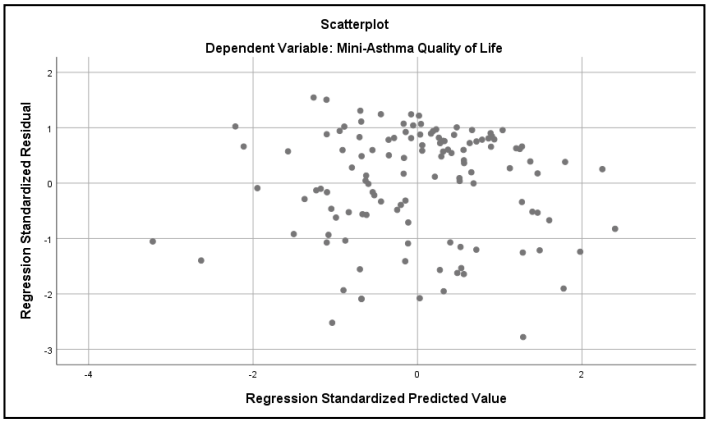
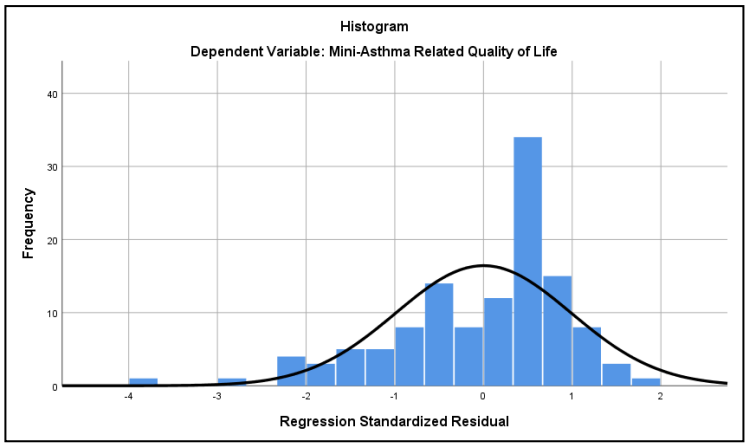


(c)

Figure C2-15: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 1 (C), including the RR, the Ti/Te and the RC_{ampexp}/AB_{ampexp}, used to predict asthma-related quality of life scores



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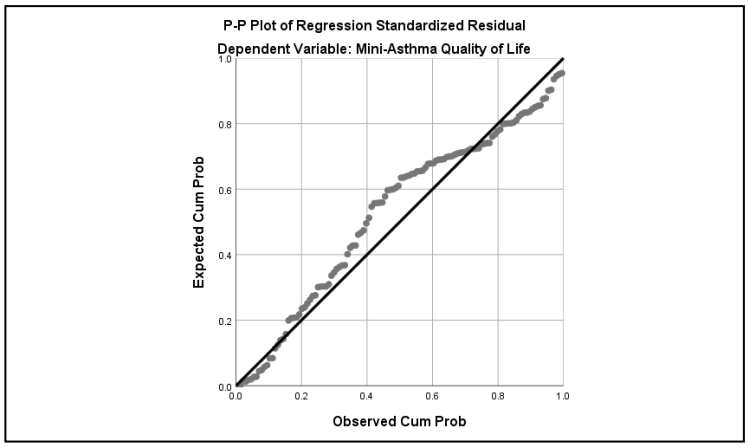

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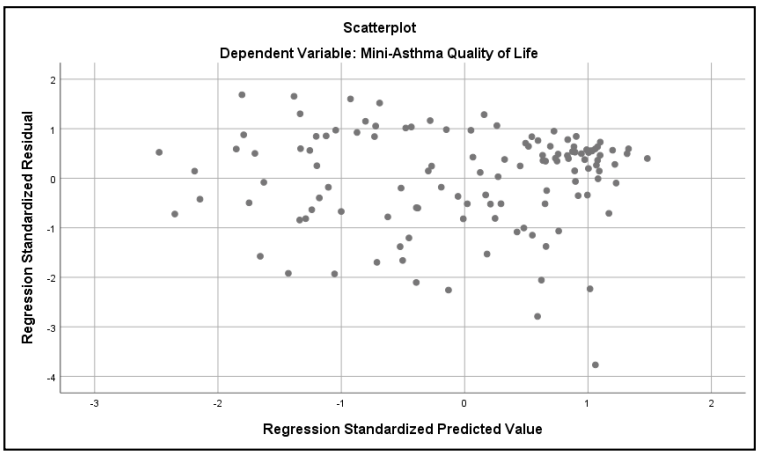

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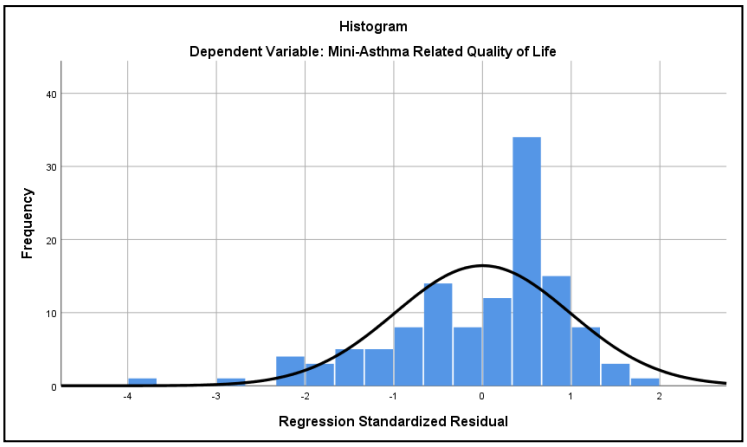
Figure C2-15: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 (C), including the %CoV of the RR, the Ti/Te and the $RC_{ampinsp}/AB_{ampinsp}$, used to predict asthma-related quality of life scores



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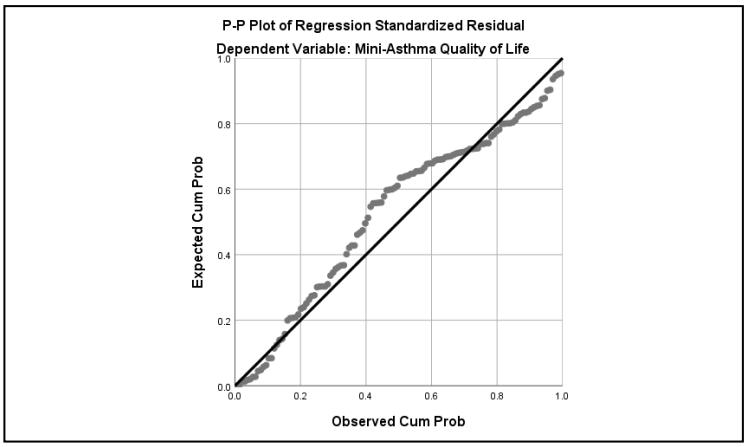

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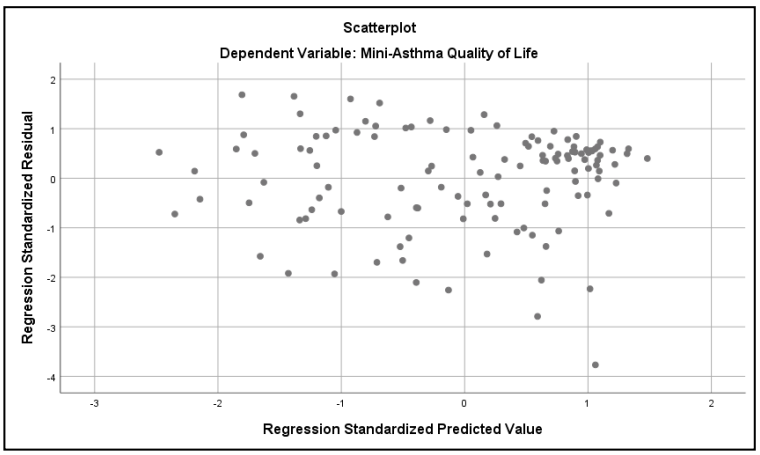

(c)

Figure C2-16: Assessment of normality of standardised residuals (plot a and b) and assumptions of homoscedasticity and linearity for regression model 2 (C), including the %CoV of the RR, the Ti/Te and the RC_{ampexp}/AB_{ampexp}, used to predict asthma-related quality of life scores

C.3 Supplemental results of the responsiveness study

Table C2-24: Results of RC_{amp}/AB_{amp} during the expiratory phase for each participant across the three recording sessions

	1st recording session		**2nd recording session**		**3rd recording session**	
Participant	***RC_{ampexp}/AB_{ampexp}**	**%$CoV_{RCampexp/ABampexp}$**	***RC_{ampexp}/AB_{ampexp}**	**%$CoV_{RCampexp/ABampexp}$**	***RC_{ampexp}/AB_{ampexp}**	**%$CoV_{RCampexp/ABampexp}$**
1	5.31	22.03	1.90	14.68	1.59	6.96
2	1.35	8.07	1.02	13.2	2.17	49.40
3	1.50	9.2	1.27	10.39	1.08	10.46
4	0.85	23.53	0.96	22.52	1.11	13.96
5	0.95	24.21	0.87	24.83	0.89	19.44
6	2.55	17.67	1.18	11.76	1.90	33.00

*mean values

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