Novel Measurements

of Cough and Breathing Abnormalities

during Sleep in Cystic Fibrosis

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Preface

The work described in this thesis was carried out in the Ludwig Engel Centre for Respiratory Research, The University of Sydney at Westmead Hospital, NSW, under the supervision of Professor John Wheatley and Associate Professor Peter Middleton. The submission of this thesis fulfils the requirements for the Degree of Doctor of Philosophy.

This is to certify that to the best of my knowledge, the content of this thesis is my own work. Some of the work in this thesis has been previously presented at the annual scientific meetings of the American Thoracic Society, European Respiratory Society and the Thoracic Society of Australia and New Zealand.

Dedication

This work is dedicated to my husband, Garrick, and our two daughters, Amelia and Charlotte.

Acknowledgements

Preparing a thesis for submission is never done without the support and encouragement of many people. During my studies, I have been fortunate to be surrounded by family, friends and colleagues who have helped and supported me. I am appreciative for the opportunities given to me to present my data at both local and international conferences on behalf of the Ludwig Engel Centre for Respiratory Research and the University of Sydney.

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Abstract

This Doctor of Philosophy thesis describes cystic fibrosis (CF), sleep parameters and novel measurement techniques to determine the effect of lung disease on sleep using non-invasive techniques.

Cystic Fibrosis (CF) is characterised by lungs that are normal at birth, but as lung disease progresses with age, adults with CF can develop sleep abnormalities including alteration in sleep architecture and sleep disordered breathing. This thesis seeks to investigate simple non-invasive measures which can detect abnormalities of sleep and breathing in CF adults. The identification of respiratory sounds (normal lung sounds, coughs, crackles, wheezes and snores) will be examined using the non-invasive sleep and breathing measurement device, the Sonomat. The characterisation of these respiratory sounds will be based on spectrographic and audio analysis of the Sonomat. Cross-sectional and longitudinal analysis of adults with CF using polysomnography and the Sonomat will further assess objective sleep and breathing abnormalities.

Additional to the examination of objective measurements of sleep, subjective evaluation using CF-specific and sleep-specific questionnaires will assess subjective sleep quality and QoL in adults with CF.

Contents

List of Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnoea Hypopnoea Index
AI	Arousal Index
ASA	Australasian Sleep Association
ASL	Airway Surface Liquid
ASTA	Australasian Sleep Technologists Association
BMI	Body Mass Index
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CF QoL	Cystic Fibrosis Quality of Life
CFTR	Cystic Fibrosis Transmembrane Regulator channel
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CSA	Central Sleep Apnoea
ECG	Electro-cardiogram
EEG	Electro-encephalogram
EMG	Electro-myogram
ENaC	Epithelial Sodium Channel

List of Abbreviations

EOG	Electro-oculogram
ESS	Epworth Sleepiness Scale
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
HACC	Hull Automatic Cough Counter
Hz	Hertz (unit of measurement)
Kg	Kilogram (unit of weight)
LCM	Leicester Cough Monitor
m	Metre (unit of measurement)
MAT AHI	Apnoea Hypopnoea Index for the Sonomat
min	Minute (unit of time)
mm	Millimetre (unit of measurement)
ms	Milliseconds (unit of measurement)
mucPSA	Mucoid *Pseudomonas aeruginosa*
O_2	Oxygen
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnoea
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index

List of Abbreviations

Qd	Quiescent Duration
QoL	Quality of Life
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
RERA	Respiratory Effort Related Arousal
s	Second (unit of measurement)
SaO_2	Oxygen saturation of haemoglobin in arterial blood
SD	Standard Deviation
SDB	Sleep Disordered Breathing
SE	Sleep Efficiency
SEM	Standard Error of the Mean
SGRQ	St George Respiratory Questionnaire
SpO_2	Peripheral capillary oxygen saturation
TRT	Total Recording Time
TST	Total Sleep Time
VAS	Visual Analogue Scale
WASO	Wake After Sleep Onset

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Publications and Abstracts

Erskine, O. J., Keatley, L., Bishop, J., Lambert, S., Wheatley, J. R., & Middleton, P. G. (2014). Polysomnography results in cystic fibrosis. Respirology, 19 (Supp.2), 111.

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CHAPTER 1: LITERATURE REVIEW

Cystic fibrosis (CF) is the most common lethal inherited disease in Australia with the carrier rate 1 in 25 and the incidence of CF in Australia was about 1 in 2800 live births (Massie et al., 2000). There have been recent advancements in the treatment, using CF transmembrane regulator (CFTR) modulator drug therapy, of the complications of CF but it still remains a progressive lung disease. Overnight oximetry and polysomnography (PSG) can be used to detect nocturnal respiration, sleep and other events. However, further, preferably non-invasive testing is required to assess other aspects of respiration including the presence of adventitial sounds.

This PhD thesis describes cystic fibrosis (CF), sleep parameters and novel measurement techniques to determine the effect of lung disease on sleep using non-invasive techniques. The review below discusses the appraisal of literature of respiratory sounds and sleep disturbances that can be found in people with CF and the reasons why this is an important area of research for these adults.

SECTION A - NORMAL VENTILATION AND BREATHING

Breathing can be defined as the process of respiration, during which air is actively inhaled into the lungs through the nose or mouth and then during normal quiet breathing expiration is due to passive muscle relaxation.

Ventilation is the process by which there is an exchange of oxygen and carbon dioxide between the lungs and the atmosphere so that oxygen can be exchanged for carbon dioxide in the alveoli.

1.1 Anatomy of the Airways – Trachea to Alveolar Sacs

After passing through the upper airways including the nose or mouth, pharynx and larynx, air enters the tracheobronchial tree. The conducting zone, the first 16 generations of the airways, comprises the airways beginning with the trachea down to the terminal bronchioles. This conducting zone, known also as the anatomic dead space, contains no alveoli and thus is incapable of gas exchange with venous blood. From the 17^{th} to 19^{th} generations, in the respiratory bronchioles, alveoli start to appear and this zone is referred to as the transitional zone. The 20^{th} to 22^{nd} generations are lined with alveoli. These alveolar ducts and alveolar sacs (23^{rd} generation), which terminate the tracheobronchial tree, are referred to as the respiratory zone, where gas exchange of oxygen and carbon dioxide takes place.

1.2 AIRWAY CELLS

The respiratory tract from the upper airway to the terminal bronchioles is lined with pseudostratified columnar epithelium, with the predominant cells the ciliated epithelial cell, interspersed with mucus-secreting goblet cells and other secretory cells. In the larger airways, the ciliated cells are pseudostratified columnar cells whilst they become cuboidal in the bronchioles. In the bronchioles, the goblet cells become less frequent and are replaced by Clara cells. These Clara cells secrete proteins (including surfactant apoproteins SpA, SpB and SpD), lipids, glycoproteins and modulators of inflammation. The ciliated epithelium, along with mucus secreted by glands along the airways, goblet and Clara cells, constitutes an important defence mechanism for the lungs termed the "mucociliary escalator". Recently, in a study published in Nature, a novel, rare cell type termed the "pulmonary ionocyte" which co-expresses *FOXI1* and *CFTR* was reported (Plasschaert et al., 2018). The authors showed that Notch signalling is necessary and *FOXI1* expression is sufficient to drive the production of the pulmonary ionocyte and they also demonstrated that the pulmonary ionocyte is a major source of *CFTR* protein activity in the conducting airway epithelium (Plasschaert et al., 2018). This discovery could be very important for CF physiology and how the cell states vary between homeostasis, injury-repair and disease.

The alveolar surface is mainly composed of a thin layer of epithelial cell, the type I alveolar cells. Type II alveolar cells are found interspersed among the epithelial cells and are thought to produce the fluid layer that lines the alveoli. The type I cells allow most of the gas exchange between the alveolar air and the pulmonary capillary blood. Along the extra-cellular lining of the alveolar surface are found phagocytic alveolar

macrophages. These mononucleated cells phagocytose inspired particles such as bacteria.

Mast cells are also found in the airways. The cells contain membrane-bound secretory granules that consist of many inflammatory mediators, including histamine, proteoglycans, lysosomal enzymes, and metabolites of arachidonic acid that can induce bronchoconstriction, stimulate mucus secretion, and induce mucosal oedema by increasing permeability of bronchial vessels.

The alveolar-capillary unit is the site of gas exchange in the lung. The alveoli are almost completely enveloped in pulmonary capillaries. There may be as many as 170 alveoli per cubic millimetre of lung parenchyma resulting in about 50 to 100 m^2 of surface area available for gas exchange by diffusion (Ochs et al., 2004).

1.3 MUCOCILIARY CLEARANCE

Mucus lining the airways comprises of two layers, an outer gel layer with trapped inspired particles and a sol layer that directly covers the ciliated epithelium. The cilia beat at frequencies between 10 and 15 Hz, and the mucus moves progressively faster as it travels from the periphery (Chilvers and O'Callaghan, 2000).

In the non-diseased state, the airways cilia beat sequentially forming metachronous waves in such a way that the mucus covering the airways is moved up the airways, away from the alveoli and toward the pharynx. The “mucociliary escalator” is an

important mechanism of defence for the lungs by assisting in the removal of particles that are found in the airways.

The airway surface liquid (ASL) is regulated by oppositely directed chloride ion and sodium ion flux (caused by osmotic gradients established by active ion transport) across the airway epithelium (Tarran et al., 2001). In CF airways this regulation is lost due to the absence of the *CFTR*-mediated chloride ion secretion and concomitant hyper-absorption of sodium ions via the epithelial sodium channel (ENaC) (Boucher et al., 1986, Stutts et al., 1995). Increased ENaC absorption contributes to dehydration of the ASL layer, the depletion of which is proposed to impair mucociliary clearance and hence reduced ability of the airways to clear bacteria and other foreign particles from the lower airways (Boucher, 2007, Goss and Ratjen, 2013b). Pezzulo et al., demonstrated that due to defects in the *CFTR* protein reduced bicarbonate secretion is seen in the airways of a pig CF model which in turn lowers the pH and subsequently reduces the respiratory epithelium's ability to eradicate bacteria from the airway surface epithelium (Pezzulo et al., 2012). In a study by Abou Alaiwa et al., acidic pH was found to reduce the activity of individual ASL antimicrobials, impair synergism between them, and thus disrupt an important airway host defence mechanism (Abou Alaiwa et al., 2014). Interestingly, airway surface liquid pH in children in vivo has not been found to be altered in CF (Schultz et al., 2017), so more studies are needed to further investigate these varied results.

In an article by Abdullah et al., following chronic exposure in primary human bronchial epithelial cultures to supernatant from mucopurulent material, there was the absence of the fluid secretory response in CF thereby producing a more dehydrated (concentrated)

mucus that was predicted to exacerbate mucus adhesion and accumulation, rather than exhibit the normal hydrating/flushing response as an adaptive host response (Abdullah et al., 2018).

1.4 NORMAL RESPIRATORY SOUNDS

Since Rene Laennec invented the first true stethoscope using a hollow wooden tube in Paris in 1816 (Laënnec, 1819, Roguin, 2006), the first seminal work on pulmonary sounds was detailed by him 3 years later, entitled "De l'auscultation mediate ou Traite du Diagnostic des Maladies des Poumon et du Coeur" (Laënnec, 1819).

Interestingly, Laennec had the idea of using a hollow tube after observing children playing in a park communicating with each other using a hollow tube and a pin scratching on one end. It was only in 1945-1946 that the ideal properties of the modern stethoscope were described by Rappaport, Sprague and Groom (Roguin, 2006). These properties included the use of a binaural stethoscope with a combination chest piece, short tubing with low internal volume and well-fitting earpieces. Over time, pulmonary sounds have been described by many authors but it is only over the past 60 to 70 years that attempts have been made to universally define these sounds based on specified criteria including time (duration and timing within the respiratory cycle), frequency or pitch and intensity or loudness (Hadjileontiadis, 2008). Normal lung sounds are particular sounds heard over specific locations of the chest during respiration of healthy subjects. It is a noise that peaks with a frequency below 100 Hz (Gavriely et al., 1981). The characteristics of normal lung sounds heard over the chest wall are the result of the nature of the sound generator and the distortion of the sound upon transmission to the

location of detection. The inspiratory component of the normal lung sound is generated primarily within the lobar and segmental airways, whereas the expiratory component comes from more proximal locations (Pasterkamp et al., 1997). Air turbulence is presumed to generate the normal lung sounds. Lung sound amplitude differs between subjects and different locations on the chest surface, but primarily varies with the square of the air flow (Pasterkamp et al., 1997).

The encasement of the pulmonary parenchyma within the rigid chest wall is an important factor that affects the way sound is propagated to the chest surface. The composition of the chest wall including ribs, muscle and skin make it a complex surface upon which to make acoustic measurements (Pasterkamp et al., 1997).

The difference in measured acceleration of approximately 20 dB between the trachea and chest wall at lower frequencies has been reported together with relative dampening of the higher frequencies during transmission to the chest wall (Wodicka et al., 1990). Recent improvements in sound analysis, measurement and processing have extended the bandwidth to more than 1500 Hz to encompass the lung sound frequency range (Lu et al., 1995). Lu at al., found that sound at higher frequencies reaches the chest wall faster than at lower frequencies. This finding indicates that respiratory sound transmission is highly dispersive, most probably owing to frequency-dependent airway and parenchymal wave speeds (Lu et al., 1995). Ultimately, this tends to dampen or muffle the higher frequency sounds more than lower frequency sounds.

1.5 ADVENTITIAL RESPIRATORY SOUNDS

Respiratory sounds, such as crackles, wheeze and squawks, have been recorded by physicians since the use of the first stethoscope developed by Laennec (Laënnec, 1819). However, the nomenclature of the sounds documented have had varying degrees of consensus among physicians. With the advent of new technology, it is now possible to record these respiratory sounds and obtain consensus regarding the characteristics of these sounds. An Ad Hoc Committee on Pulmonary Nomenclature was formed in the US and their report published in 1977 (Cugell et al., 1977) in an attempt to provide consensus statements on respiratory sound nomenclature. The Ad Hoc Committee on Pulmonary Nomenclature recommended using the term crackles to describe discontinuous lung sounds instead of the previous term, "rales" or "crepitations". For high-pitched continuous sounds, the term wheeze was recommended. For low-pitched continuous sounds, the term "rhonchi" was suggested (Cugell et al., 1977). Further to this, expert respiratory physicians, engineers and physiologists held the 10th International Lung Sounds Association meeting in Tokyo in 1985 to review the current pulmonary sound nomenclature and provide recommendations for terminology in various languages including: English, French, German, Japanese, Portuguese and Spanish (Mikami et al., 1987). Again following the suggestions first made by Robertson and Coope in 1957 in the Lancet (Robertson and Coope, 1957), the symposium in Tokyo divided adventitious sounds into 2 major categories: continuous sounds or discontinuous sounds. The sounds can be further defined based on their physical properties (frequency, durations, initial deflection width) (Mikami et al., 1987).

Pulmonary pathology can clearly affect the amplitude and timing of sound transmission from the airways to the chest surface. In patients with emphysema, a decrease (Ploysongsang et al., 1982) and larger variability of transmitted amplitude at low frequencies was observed, which is qualitatively consistent with the common auscultatory finding of decreased lung sound intensity. In bronchial obstruction, such as seen in patients with asthma, an increase of higher frequency components of the sound spectrum can be seen without the appearance of wheeze; then during bronchodilation, the sound energy moves back to lower frequencies (Malmberg et al., 1994). Increased non-musical breath sounds heard on both phases of the respiratory cycle can be suggestive of focal consolidation (Bohadana et al., 2014).

Another method of sound classification uses sensors for lung sound recording. Two main types of sensors commonly used include: small microphones and accelerometers. Small microphones can come in different sizes and shapes which can affect the overall frequency response of the coupling chamber used in the microphone.

Those microphones which are smaller and conically shaped have been found to be more sensitive to higher lung sound frequencies as described by Kraman et al. (Kraman et al., 1995). The optimal electret microphone couple chamber was found to be conical in shape, between 10 and 15 mm in diameter at the skin, and either not vented or vented with a tube no wider than 23 g or shorter than 20 mm (Kraman et al., 1995).

Contact accelerometers are also able to be used to record lung sounds. They can be calibrated on a vibration table so their output is quantified. However, usually they are more expensive than microphones, are often fragile, and may exhibit internal

resonances near the lung sound frequencies of interest (Pasterkamp et al., 1997). Pasterkamp et al. examined the differences between contact and air-couple sensors and found that there was a high susceptibility to artefacts by noise from cable movements with the contact sensors (Pasterkamp et al., 1993)

The development and widespread application of the Fast Fourier Transform (FFT) has made frequency analysis of sounds simpler, faster, more accurate, and less expensive than previously used methods such as phonopneumography (Loudon and Murphy, 1984).

Time domain analysis has been more widely applied to the study of discontinuous sounds, whereas frequency domain has been used to study continuous sounds (Loudon and Murphy, 1984).

These findings were supported by the review of Pasterkamp et al., which supports the hypothesis that transmission of sound at low frequencies occurs at slower speeds primarily through parenchyma, whereas higher frequency sound travels through a faster, presumably more airway predominant route, as is the case in isolated lung preparations where the parenchyma and trachea are not in contact (Pasterkamp et al., 1997, Patel et al., 1995, Rice and Rice, 1987). Patel et al. found that the phase delay of sound propagation to the posterior chest surface is frequency-dependent, with shorter delays of approximately 1ms at frequencies near 1500 Hz compared with roughly 2.5 ms or more at frequencies below a few hundred Hz (Patel et al., 1995). There is also asymmetry in phase delays between the left and right posterior chest surface, and the phase delay to lower lung sites is greater than to upper sites at frequencies below 300 Hz (Patel et al., 1995). There are relatively decreased delays to the left posterior chest

surface (ie sound propagation to the left is faster), as compared with the right (Patel et al., 1995). Thus, the heterogeneous anatomy of the thorax affects both the amplitude and phase delay of sound transmission in a manner that is frequency-dependent.

Conventional Stethoscope

Analysis of pulmonary sounds can be achieved firstly by listening to sounds at the body surface. The binaural stethoscope with a combination chest piece, tubing with low internal volume and well-fitting earpieces was developed based on the ideal properties required for auscultation as detailed in the 1940s by Rappaport, Sprague and Groom (Roguin, 2006). The classic stethoscope conducts sound through hollow tubes from a pliable diaphragm in contact with the skin of the chest of the patient and the ears of the physician. The stethoscope does not provide a frequency-independent transmission of sounds. Rather it selectively amplifies or attenuates sounds within the spectrum of clinical interest (Pasterkamp et al., 1997).

Electronic Stethoscope

The latest tool in auscultating pulmonary sounds is the use of computer technology to perform analysis of lung sounds using an electronic stethoscope with digital recording capabilities to create computer visualisation of sounds converting them to time, frequency and intensity variables for further analysis and the option to record respiratory sounds for later comparison.

Electronic stethoscopes have been available for more than 30 years, but with the introduction of digital techniques, they can now allow visual display of sounds in both standard waveform and spectral formats using computer based software programs. Prior to this, electronic stethoscopes could only amplify the acoustic signals including background noise (Bank et al., 2016). As more research has been conducted using digital sound analyses, widely accepted concepts based on the classic stethoscope have been challenged. In a paper by Pasterkamp et al., analyses of wheezes were so subjective that the inter-observer and intra-observer variability was described as somewhere "between chance and total agreement", whereas the computer analysis they used allowed reproducible and objective characterisation of wheezing in patients with asthma (Pasterkamp et al., 1987). Inspiratory sounds measured simultaneously over the extra-thoracic trachea and at the chest surface contain highly unique regional information that can be reproducibly extracted with a knowledge of the breathing flow rate (Pasterkamp et al., 1997).

As an added advantage, the electronic stethoscope allows the physician to record heart or lung sounds of their patient directly onto their computer for further visualisation and analysis. These sounds can also be used to calibrate and characterise the sounds allowing multiple users to listen to the same sound. Leng et al. examined a number of stethoscopes including the Thinklabs Rhythm 32 stethoscope which uses an electromagnetic diaphragm with a conductive inner surface to form a capacitive sensor. This diaphragm responds to sound waves identically to a conventional acoustic stethoscope, with changes in an electric field replacing changes in air pressure. This preserves the sound of an acoustic stethoscope with the benefits of amplification (Leng et al., 2015).

Sonomat

The non-invasive recording device, the Sonomat, by use of product specific software, has the potential to record and characterise respiratory sounds such as crackles, cough and wheeze. Using an inbuilt microphone, the Sonomat can record cough. The microphone can then be used to manually score respiratory sounds, including cough, crackles and wheeze. At this time, the sounds need to be manually scored, however, new validation studies performed at the David Read Laboratory are investigating automated methods (Norman et al., 2009b, Norman et al., 2014).

1.6 COUGH

Definition of Cough

A clear definition of cough is lacking in many scientific papers, and if there is a definition, none is consistent. In a consensus statement by the European Respiratory Society (ERS), the authors have recommended that all basic scientific articles should refer to cough as a three-phase motor act (Morice et al., 2007). This three phase expulsive motor act is characterised by: 1. An inspiratory effort (inspiratory phase); 2. Followed by a forced expiratory effort against a closed glottis (compressive phase); 3. Then opening of the glottis and rapid expiratory airflow (expulsive phase) (Morice et al., 2007). In particular, the ERS has recommended that for the purposes of acoustic recordings in clinical studies, cough should be described as a forced expulsive manoeuvre or manoeuvres against a closed glottis that are associated with a characteristic sound or sounds (Morice et al., 2007).

Pathophysiology of cough

During sleep, mucociliary clearance from the lungs decreases in both normal subjects (Bateman et al., 1978), and those with airways disease (Hasani et al., 1993). There have been relatively few studies investigating cough during sleep due to difficulties in measuring cough. Smith et al. looked at 19 adult patients with a pulmonary exacerbation and performed daytime and overnight sound recordings with 13 of the patients having repeat recordings prior to discharge (Smith et al., 2006). They found that cough rates fell with treatment of the pulmonary exacerbation and coughing virtually stopped overnight by discharge (Smith et al., 2006). These findings are in contrast to Hamutcu et al., who found that in children with CF, treatment of a pulmonary exacerbation did not improve either subjective (using cough score and visual analogue scores) or objective (using an ambulatory cough recording device) measures (Hamutcu et al., 2002).

Frequency of nocturnal coughing in children with CF has been shown to be higher than described for normal children (van der Giessen et al., 2009). As expected, nocturnal cough was more severe in children with more advanced lung disease (van der Giessen et al., 2009). Nocturnal cough has been studied in 10 patients with severe chronic bronchitis and emphysema and it was reported that coughs during true sleep were rare and hence cough was found to be normally suppressed during sleep and only rarely wakened patients (Power et al., 1984)

Similarly, cough has been shown to substantially reduce during sleep even during acute cough due to an upper respiratory chest infection with objective cough frequency rates

at 19 cough per hour during the day and 1.7 cough per hour during the night (Sunger et al., 2013).

Whilst in the normal healthy lung these changes are of relatively little consequence, they may impact on sleep during an upper respiratory tract infection, when sleep is fragmented by the recurrent arousals induced by the need to cough (Dobbin et al., 2005). These above studies have showed varied results investigating cough during sleep and although in text books it is written, few papers have actually measured it. This thesis seeks to further investigate the presence or absence of coughs particularly during sleep in adults with CF.

Measurement of Cough

Currently, no standardised method of cough monitoring exists. No single cough monitor is thought to be the "gold standard". There are a number of available methods of recording: automation of the cough recognition system, the Hull Automatic Cough Counter (HACC) (Barry et al., 2006); Leicester Cough Monitor (LCM) (Birring et al., 2008); and ambulatory cardiorespiratory monitoring system using the Lifeshirt^{TM} (Coyle et al., 2005, Goodrich and Orr, 2009).

The HACC uses digital signal processing to calculate characteristic spectral coefficients of sound events, which are then classified into cough and non-cough events by the use of a probabilistic neural network (Barry et al., 2006). Then the determination of the number of coughs inside each cough event was carried out by a human listener. The HACC followed by using a graphical user interface showed that for an one hour

recording, analysis took only one minute and thirty five seconds, with a sensitivity of 80 % and specificity of 96 % compared with manual audio recording (Barry et al., 2006).

The Leicester Cough Monitor developed by Birring et al., detects cough using an automated cough recorder capable of recording for 24 hours (Birring et al., 2008). The LCM was shown to have a sensitivity of 91 % and a specificity of 99 % for detecting cough in comparison with manual cough counts (Birring et al., 2008).

Coyle et al., demonstrated that the Lifeshirt^{TM} showed a high level of accuracy and agreement (kappa = 0.807) with overall sensitivity of 78 % and specificity of 99 % compared with video surveillance for the measurement of day-time and night-time cough in COPD patients (Coyle et al., 2005). The Lifeshirt^{TM} used a specialised software algorithm to identify cough (Coyle et al., 2005).

SECTION B - SLEEP

1.7 INTRODUCTION TO SLEEP

Sleep is a necessary behavioural state that occurs in every individual. However, sleep is different in every individual. In addition, disease states can alter sleep architecture and result in sleep fragmentation and arousals.

Within sleep, two separate states have been defined on the basis of a constellation of physiologic parameters. These two states, rapid eye movement (REM) and non-REM (NREM) are distinct from one another as each are from wakefulness (Kryger et al., 2016). NREM sleep is divided into 3 stages: N1 sleep, N2 sleep and N3 sleep (slow wave sleep) and R is used to name REM sleep as per the AASM terminology (Iber et al., 2007). The electroencephalogram (EEG) pattern in NREM sleep is commonly described as synchronous, with characteristic waveforms such as sleep spindles, K-complexes and high-voltage slow waves. The NREM stages closely parallels a depth of sleep continuum, with arousal thresholds generally lowest in N1 sleep and highest in N3 sleep (Kryger et al., 2016). In contrast, REM sleep is defined by EEG activation, muscle atonia, and episodic bursts of rapid eye movements (Kryger et al., 2016).

In normal healthy adults, sleep is entered through NREM sleep and REM does not occur until after approximately 80 minutes, and NREM and RM sleep alternate through the night, with an approximately 90-minute cycle. N3 sleep predominates in the first third of the night and is linked to the initiation of sleep and the length of time awake. REM sleep predominates in the last third of the night and is linked to the circadian rhythm of the body temperature (Kryger et al., 2016). Wakefulness in sleep usually accounts for

less than 5 % of the night, with NREM sleep constituting 75 - 80 % of sleep and REM sleep accounting for 20 – 35 % of sleep, occurring in 4 to 6 discrete episodes (Kryger et al., 2016)

Sleep disturbances are commonly reported by patients with chronic respiratory disease. Sleep disruption can contribute to impaired daytime functioning and overall quality of life (Bouka et al., 2012, Dancey et al., 2002, Fauroux et al., 2012, Milross et al., 2002).

1.8 Respiratory Events During Sleep

An apnoea is a period during sleep where there is no breathing. In the updated revision of the 2007 AASM Manual for the Scoring of Sleep and Associated Events, an apnoea in adults was defined as a drop in the peak airflow measurement by ≥ 90 % of pre-event baseline using an oro-nasal thermal sensor or an alternative apnoea sensor for ≥ 10 seconds (Berry et al., 2012). Hypopnoea in adults is scored when the peak airflow signal excursions drop by ≥ 30 % of pre-event baseline using nasal pressure or an alternative sensor for ≥ 10 seconds in association with either ≥ 3 % arterial oxygen desaturation or an arousal (Berry et al., 2012). However, it should be noted that in Australian laboratories, guidelines proposed by ASTA/ASA are used (Thornton et al., 2011). The apnoea definition remains used by the ASTA/ASA (Thornton et al., 2011), which is a period of ≥ 10 seconds where there is cessation of breathing. For an hypopnoea, the definition is a 50 % reduction in airflow accompanied by an arousal or a fall in oxygen saturation of 3 % or more (Thornton et al., 2011).

There have been multiple attempts of scoring snoring during sleep but none is widely used. Even in the position statement by ASTA/ASA, definitions of snoring were absent. Details have been suggested regarding the recording of snoring sound by microphones, piezo sensors or ambient sound pressure level – decibel meters but no definitions are made to assist the sleep technician in scoring snoring sounds (Thornton et al., 2011). In the Westmead laboratory, recorded sound signals from the room microphone were analysed. Previous studies from our laboratory have defined snore sounds but did not describe other sounds, such as a cough (Lee et al., 2008). A snore sound was defined as an obvious deflection from background sound level (with no minimum decibel threshold), which was in-phase with inspiration and occurred during sleep (Lee et al., 2008). Each individual snore was manually scored, and a score index (snores per hour of sleep) was calculated. Each 30 second sleep epoch that contained 3 or more snore sounds was classified as a "snoring epoch". The total number of "snoring epochs" was then expressed as a percentage of the total number of sleep epochs (snoring sleep time) (Lee et al., 2008).

1.9 SLEEP DISORDERED BREATHING (SDB)

Using the International Classification of Sleep Disorders (ICSD), sleep-related breathing disorders span a spectrum including disorders resulting in upper airway obstruction during sleep, disorders that alter breathing patterns, and disorders that produce hypoventilation or hypoxaemia (Sateia and Hauri, 2005).

The severity of sleep related obstructive breathing events has been described as follows:

- Mild: 5-15 events per hour
- Moderate: 15 to 30 events per hour

- Severe: greater than 30 events per hour (Flemons et al., 1999)

Lower airway dysfunction is not considered in these guidelines. Interestingly, the American Academy of Sleep Medicine (AASM) recommendations for syndrome definition of sleep disordered breathing made no mention of arousal from sleep due to coughing, sneezing or grunting (Flemons et al., 1999). It was likely that criteria can be developed to separately classify cough arousals, and that these could become routinely measured in patients with chronic lung disease who undergo sleep studies.

1.10 SLEEP MEASUREMENT

Introduction

Sleep may be measured using subjective or objective methods. Sleep is most reliably objectively measured using in-laboratory polysomnography (PSG), which continuously measures a series of physiological variables, including the EEG and electro-oculogram (EOG) to assess sleep stages, nasal flow, oximetry and body posture to assist in assessment of arousals and oxygen saturation during the night. The "gold standard" of sleep measurement remains in-laboratory polysomnography. However, due to the increasing prevalence of sleep disorders, home-style sleep studies are emerging in the field of sleep measurement. In-laboratory sleep studies can create an artificial environment for subjects and recording sleep at home may allow the subject to sleep better in their own home environment. Detailed descriptions of the methods used for polysomnography and the Sonomat are in Chapter 2 – Methods.

Diagnostic polysomnography

In-laboratory polysomnography (PSG), measures a series of variables including the electro-encephalogram (EEG), electro-oculogram (EOG), electro-myogram (EMG), respiratory effort using inductive plethysmography, oxygen saturation in addition to a room microphone used to record sound events (Iber et al., 2007, Thornton et al., 2011)

Particularly for this project, recording of respiratory sounds was important if we were to analyse these abnormalities in the CF population. In the AASM guidelines, microphones for snoring sound were recommended with a sampling frequency of 500 Hz (Iber et al., 2007). Good sensitivity in the range of 20 Hz to 3 KHz was recommended (Iber et al., 2007). In Australian sleep laboratories (as in our sleep laboratory), decibel (sound level) meters are commonly used. These sound meters measure the ambient sound pressure level within the bedroom and provide a quantitative validated measure of the sound which can be compared with environmental noises.

Sonomat

A simple system to address limitations for in-laboratory PSG has been developed called the Sonomat (Norman et al., 2014, Norman et al., 2009a, Norman et al., 2009b). The Sonomat is a new, non-invasive recording device which can document sleep and breathing parameters at home using a portable mat which sits on top of the patient's mattress, underneath the sheets (Norman et al., 2009b). The mat contains two room microphones and four highly sensitive vibration sensors, strategically positioned to

detect breath sounds, breathing movement and body movement, giving both respiratory and arousal information, allowing calculation of numbers of breathing and movement arousals through the night. All variables are recorded and stored directly on a SD card within the Sonomat. This makes the Sonomat the ideal system to perform repeated overnight studies over a number of weeks at home and has been used in different patient groups (Johnson et al., 2011, Ngiam et al., 2011, Norman et al., 2009a, Norman et al., 2009b).

The Sonomat has been previously validated in subjects with a clinical history of OSA (Norman et al., 2014). There were positive correlations between the PSG and Sonomat for measures of sleep time, respiratory events and the AHI (all correlations > 0.89) (Norman et al., 2014).

SECTION C - CYSTIC FIBROSIS

1.11 INTRODUCTION TO CYSTIC FIBROSIS

Cystic Fibrosis (CF), the most common lethal inherited disorder in Australian, affects 1 in 2,800 live births (Massie et al., 2000). CF is caused by defects in a single gene on the long arm of chromosome 7 encoding a protein, the cystic fibrosis transmembrane regulator (CFTR), which primarily functions as a cyclic adenosine monophosphate-regulated chloride channel. The CF gene was successfully identified in 1989 in a collaborative effort by the groups of Lap-Chee Tsui and John O'Riordan at Toronto's Hospital for Sick Children, together with Francis Collins at the Howard Hughes Medical Institute at the University of Michigan (Kerem et al., 1989, Riordan et al., 1989, Rommens et al., 1989). It is thought that dysfunction of the CFTR protein alters the balance of chloride secretion and sodium absorption to an absorptive state that results in airway surface dehydration (Boucher, 2007). Airway surface liquid depletion has been proposed to impair mucociliary clearance and reduce ability of the airways to clear bacteria and other foreign particles from the lower airways (Goss and Ratjen, 2013b).

CF is characterised by lungs that are normal at birth, but with increased inflammation and infection within the first year (Ranganathan et al., 2017). The primary cause of morbidity and mortality in CF is chronic endobronchial infection associated with an intense host inflammatory response leading to progressive airway destruction (Ramsey and Boat, 1994, Rosenfeld et al., 2001). Although infection remains the major trigger of airway inflammation in CF, the response to any pro-inflammatory stimuli is altered

in CF, and neutrophil dominated inflammation persists in the majority of patients (Goss and Ratjen, 2013a). Sagel et al., have demonstrated that neutrophil elastase has predictive value for subsequent lung function decline in CF and longitudinal changes in sputum biomarkers are related to lung function changes (Sagel et al., 2012). That is, that higher baseline neutrophil elastase concentrations were associated with faster rates of decline in forced expiratory volume in one second (FEV_1) % predicted (Sagel et al., 2012). Being able to identify biomarkers which can predict and monitor disease progression could have a significant impact on clinical regimens in CF patients.

Risk factors for decline in FEV_1 in paediatric patients included female gender, pancreatic insufficiency, poor nutritional status, and infection with *Pseudomonas aeruginosa* (Konstan et al., 2007). In addition, crackles, daily sputum production, wheezing, sinusitis, number of pulmonary exacerbations treated with IV antibiotics and elevated liver function tests were found to be additional risk factors for FEV_1 decline in children (Konstan et al., 2007). Further to this study in children, the risks factors in adults were explored by this group, however, daily cough was found to be associated with decline only in the younger adults (age 18 – 24 years) but not in the older adults (age ≥ 25 years) (Konstan et al., 2012). In final multivariate models, statistical significance of factors in the younger age group (age 18 – 24 years) included: female gender; baseline FEV_1 % predicted; daily cough; sinusitis; pancreatic enzyme use; mucoid *P. aeruginosa*; multidrug-resistant *P. aeruginosa*; *B. cepacia* (Konstan et al., 2012). In contrast, the only factors that were found to be statistically significant in the older age cohort (≥ 25 years) were: baseline FEV_1 predicted, sinusitis and pancreatic enzyme use (Konstan et al., 2012). These authors discussed the reason that some factors were not found to be significant may be that in adult patients, the risk factor (eg

crackles) has been present for an extended period of time and the disease progression associated with its onset has already occurred (Konstan et al., 2012).

1.12 DIAGNOSIS

In NSW, new born screening was introduced in 1981, with the other states progressively undertaking newborn screening such that now 60 % of all new diagnoses of CF are made by newborn screening (NBS) (Ruseckaite et al., 2018). Meconium ileus was reported in 5.6 % of cases, gastrointestinal symptoms were reported in 11.1 %, and respiratory symptoms in 9.7 % (Ruseckaite et al., 2018). Early diagnosis is associated with improved health outcomes in these patients (Southern et al., 2009). As of December 2016, 49.3 % of all CF patients were homozygous for F508del and 42.9 % were compound heterozygous F508del (Ruseckaite et al., 2018). The genetic mutation F508del, G551D or G542X was present in nearly 95 % of CF patients (Ruseckaite et al., 2018)

1.13 PREVALENCE

In Australia, the incidence of CF is about 1 in 2,800 live births (Massie et al., 2000). Approximately 1 in 25 Australians are carriers of a genetic mutation responsible for CF (Massie et al., 2007). As of December 2016, the median age of patients with CF was 19.3 years with the proportion of adults in the CF Registry in Australia at 53.2 % (Ruseckaite et al., 2018)

1.14 SYMPTOMS

At birth, CF can manifest in a number of ways including presentation with meconium ileus, failure to thrive, reduced or stunted growth or recurrent chest infections, particularly if the child's diagnosis is delayed. As the disease progresses, lung function, failure to thrive or abdominal issues may worsen and if not treated correctly result in irreversible disease. Various methods have been employed, such as CT-detected structural lung disease, in an attempt to intervene early to reduce the progression, severity and disease burden later in life (Newbegin et al., 2018a)

Daytime cough

Those people with CF who have established lung disease often will have a daily cough, particularly in the mornings. Even though airway clearance can reduce cough, it is often still present. One of the hallmark features of a pulmonary exacerbation is the presence of increased cough. Cough is well known to occur on a regular basis in those with mild, moderate, and severe lung disease but quantitative studies (day or night) have only recently been started. A recent cross-sectional study using an ambulatory recording device has documented frequent coughing in CF adults (Kerem et al., 2011). However, no long-term studies have examined the use of cough recorders to determine if increasing cough is the earliest abnormality in a CF adult developing a pulmonary exacerbation.

The subjective reporting of cough is less reliable than objective measures. Increased cough frequency and duration comprise some of the common symptoms associated with pulmonary exacerbations in people with CF (Dakin et al., 2001, Fuchs et al., 1994).

Cough is commonly used as an objective measure in clinical studies of CF patients. A recent study using the Lifeshirt™, a portable cough monitoring device, has documented the circadian variability of cough in CF adults, showing a median of 41 coughs per hour while "awake", compared with 2 coughs in the nocturnal part of the study (Kerem et al., 2011). But the definition of "sleep" in this study was based on body position and breathing pattern. No measure of the resultant sleep fragmentation was made, nor any quantitative or even semi-quantitative measure of the forces involved in the coughs – it was just recorded as the presence of cough. Finally, these ambulatory cough recorders will not record other features of sleep disordered breathing such as grunting, snoring, increased respiratory effort, nor hypoventilation. Something that is simple, non-invasive and can be used on a nightly basis to measure sleep-cough and resultant arousals would be required to help predict pulmonary exacerbations. Hence, the portable Sonomat device may be useful to measure these sleep disturbances in CF people.

As noted above, increased cough frequency is a common symptom of an impending pulmonary exacerbation. In an attempt to objectively monitor cough in children with CF, Hamutcu et al examined 14 children with CF using an ambulatory cough recorder (LR100 cough recorder) and a conventional tape recorder (Hamutcu et al., 2002). These authors found no significant correlation between admission, discharge cough objective scores, day or night-time cough scores, nor day or night time visual analogue scores

(VAS) (Hamutcu et al., 2002). In addition, they did note that there was no improvement between admission and discharge scores despite increases in spirometry (Hamutcu et al., 2002). These results may be affected by the small number of subjects studied and the fact that the authors measured the numbers of cough epochs and not the duration of the individual epoch which may correlate better with patient perception of cough as the patients may notice long coughing bouts rather than the number of cough epochs more.

In 19 adult CF subjects (median age of 23 years), cough sound recordings were obtained using a digital recording device whilst patients were admitted with a pulmonary exacerbation (Smith et al., 2006). Manually scored coughs fell significantly by 51 % ($p < 0.001$) during daytime and 72 % ($p = 0.049$) during night time over the course of the admission (Smith et al., 2006). Only the change in night VAS correlated with change in objective cough rates ($p = 0.001$). The change in VAS during the day did not correlate with change in objective day cough rate ($p = 0.070$). However, the length of cough epochs during the day and night significantly reduced with treatment ($p = 0.009$) (Smith et al., 2006). However, this was arduous task as each recording took approximately 2.5 to 3 hours to process and the subject had to put on a bulky vest device to measure the coughing. This suggests that there is a need for an automated system that is compatible with day to day living to measure such parameters such as night time and daytime cough.

Nocturnal cough

Anecdotally, it is often noted by the patient's partner or parent that the patient's breathing during sleep worsened a few days before the patient was first aware of a

developing exacerbation. An increase in arousals in the nights before an exacerbation (according to Fuch's criteria) may well be the key to early recognition of an impending exacerbation (Fuchs et al., 1994). The current research will examine cough and other respiratory disturbances and their resultant sleep fragmentation in CF patients; as part of the longitudinal study, nocturnal sleep disordered breathing before and after exacerbations will be investigated. The changes in sleep in CF adults may be able to determine an earlier abnormality seen during the evolution of a pulmonary exacerbation.

1.15 PULMONARY EXACERBATIONS

A person with CF will develop periods when they have more cough, more sputum, feel unwell and may lose lung function capacity, as an exaggerated response to chest infections. These are clinically termed "exacerbations" and treated with antibiotics, but the exact definition of a pulmonary exacerbation varies widely. The most commonly used definition in people with CF is the definition used initially by Fuchs et al. during their treatment trial of aerosolised recombinant human DNase and proposed that a pulmonary exacerbation was reported to have occurred in patients with any 4 of the following 12 signs or symptoms and in whom patients subsequently required intravenous antibiotics (Fuchs et al., 1994). The 12 parameters included: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue or lethargy; temperature above 38 degrees Celsius; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent or more from a previously

recorded value; or radiographic changes indicative of pulmonary infection (Fuchs et al., 1994).

Clinical treatment regimens for CF have outlined the need for early intervention to lessen the number and severity of pulmonary exacerbations, which in turn, lessen the loss of pulmonary function and delay the onset of respiratory failure and death (Doring et al., 2012). It has been shown that one quarter of CF patients treated with antibiotics for acute exacerbations did not recover to baseline function (Sanders et al., 2011). Therefore, the early recognition and treatment of pulmonary exacerbations is critical to further improvements in CF survival (Newbegin et al., 2018b, Ranganathan et al., 2017). However, despite improvements in therapy for CF, death from respiratory failure still occurs in > 90 % of patients (Bell et al., 2011).

For shorter duration or milder pulmonary exacerbations, many will spontaneously resolve leading to the difficulties in the definition of an exacerbation as outlined above (Abbott et al., 2009). For those exacerbations that are slightly more severe or lasting longer, then oral and / or nebulised antibiotics may be sufficient treatment, but for longer duration and more severe exacerbations, intravenous antibiotics in hospital are often necessary (Flume et al., 2009b, Goss and Ratjen, 2013b).

Whilst the onset of a CF exacerbation is usually thought to occur over 1-2 days, this is generally based on the patient's recognition of their symptoms (Ferkol et al., 2006, Goss and Burns, 2007, Goss et al., 2009). Many authors are proposing a clinical paradigm to detect an earlier abnormality in the onset of a pulmonary exacerbation in CF (Bilton et al., 2011, Dakin et al., 2001). Simple peak flow measurements, like those used in asthma, are unlikely to be useful for CF as mild and moderate exacerbations can occur

with relatively little change in peak flow or spirometry. Previous authors have found that the value of symptoms in identifying pulmonary exacerbations is high but performing daily symptom cards may be hard for the subject and not necessarily a sensible option for long-term use (Dakin et al., 2001).

An alternative method of evaluating pulmonary exacerbations may be identification of respiratory sounds, such as coughs or crackles, which indicate sputum retention. These respiratory sounds can be measured day and night to identify changes in impairment of airway functioning signifying a possible pulmonary exacerbation due to difficulty clearing mucus. Optimising non-invasive measurements of markers to predict the onset of an exacerbation would be useful to the long-term management of people with CF.

SECTION D - SLEEP AND CYSTIC FIBROSIS

1.16 INTRODUCTION TO SLEEP AND CYSTIC FIBROSIS

Disease states can alter sleep architecture and result in sleep fragmentation and arousals. As lung disease worsens with age, adults with CF develop worsening sleep disordered breathing (SDB) (de Castro-Silva et al., 2009, Fauroux et al., 2012, Katz, 2014, Milross et al., 2004, Veronezi et al., 2015).

Advances in sleep medicine have enabled in-depth parameters of sleep to be analysed in a wide variety of medical conditions. Patients with CF may be predisposed to poor sleep quality due to a variety of factors including upper and lower airway abnormalities and impaired ventilation and perfusion. Furthermore, other contributors to CF sleep abnormalities may include medications, constipation, gastro-oesophageal reflux, chronic anxiety or depression.

As noted above, patients with CF produce increased sputum volume each day, even when they have relatively mild lung disease. As mucociliary clearance is reduced during sleep (Bateman et al., 1978), the secretions produced through the night will gradually accumulate in the airways until they provide such a strong stimulus to cough that an arousal from sleep is induced. As part of this arousal, the cough threshold is reduced sufficiently to allow the subject to cough. In patients with suppurative lung disease, such as CF, the increase in nocturnal cough is such that they cannot wait until morning, and must awaken through the night to cough and clear retained secretions. This may impact on sleep long term, even during periods of clinical stability. There

have been a number of studies investigating sleep abnormalities in subjects with CF (Dobbin et al., 2005, Milross et al., 2004, Milross et al., 2001b), but none have investigated using non-invasive methods such as the novel Sonomat, which is a portable device used to record sound and movement parameters in a mat that sits on top of the patient's mattress with no attachments to the patient.

As part of this research, sleep parameters will be examined, in particular the presence of sleep fragmentation due to cough, in adults with CF with normal lungs and those with mild, moderate and severe disease during periods of clinical stability.

Faroux et al. researched 25 children and 55 young adults with CF and showed that people with CF exhibited poor sleep quality with impaired sleep efficiency but this did not predict nocturnal gas exchange (Fauroux et al., 2012). However, nocturnal hypoxaemia was shown to occur in 20% of subjects and nocturnal hypercapnia in 47% of subjects (Fauroux et al., 2012).

Nocturnal hypoxaemia often occurs prior to daytime abnormalities of gas exchange (Perin et al., 2012). Furthermore, worsening hypercapnic respiratory failure, as a marker of pulmonary deterioration, has been strongly linked with reduced survival (Kerem et al., 1992).

In a home based study of CF subjects, recruited from a Chicago CF Clinic, using wrist actigraphy for 14 days and questionnaires, it was demonstrated that stable CF patients have disrupted sleep and higher PSQI scores than control subjects (Jankelowitz et al., 2005). These authors also found a significant correlation of fragmentation index

(measure of restlessness calculated by summing the percentage of minutes spent moving with the percentage time spent immobile per minute) with FEV_1 and PSQI scores (Jankelowitz et al., 2005).

Dobbin et al. demonstrated that during hospitalisation for an exacerbation, adults with CF had worse sleep: sleep quality, sleep efficiency, time in REM and time in slow wave sleep were all significantly reduced (Dobbin et al., 2005). Restudying this group 10 to 14 days after the initial study, demonstrated that virtually all these abnormalities had improved after a course of intravenous antibiotics (Dobbin et al., 2005). Whilst this study clearly demonstrates improvement in PSG following 2 weeks of intensive therapy, the time course of deterioration before the start of an exacerbation is currently not known. Given anecdotal data that partners / parents notice night-time cough a few days before an adult with CF notes their own exacerbation, it is likely that changes in night-time parameters occur at least a few days before clinical recognition. Parallel to the earlier intervention in asthma exacerbations, analysing reliever use rather than clinical symptoms, and earlier recognition of deterioration may offer therapeutic options before clinical status worsens significantly (Busse et al., 2008).

A cross-sectional study performed in adults with CF when clinically stable was undertaken by Perin et al., 2012 to investigate what are the best predictors of sleep desaturation in CF patients (Perin et al., 2012). These authors studied 51 clinically stable CF subjects (FEV_1 ranged from 115 % to 19.5 % of predicted, mean 57.7 % ± 24.7 % of predicted) and 25 age-matched healthy control subjects and found CF patients had impaired subjective sleep quality with a higher Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) scores than controls ($p = 0.002$ and $p <$

0.001, respectively) (Perin et al., 2012). They demonstrated a significant difference between CF subjects and controls in ESS with 26 % of the CF subjects reporting an ESS of more than 10 versus 8 % of control subjects ($p < 0.001$) (Perin et al., 2012). Overnight polysomnography demonstrated a higher arousal index in the adults with CF compared with healthy age-matched controls (12.1 ± 6.1 events per hour vs 8.9 ± 4.7 events per hour, $p = 0.02$) (Perin et al., 2012). Interestingly, sleep efficiency was similar in the groups (81.1 ± 11.9 vs 82.0 ± 7.8 %, p = NS) and AHI was normal in both groups (0.3 events per hour in CF group vs 0.5 events per hour in control group, NS) (Perin et al., 2012).

There were statistically significant differences in oxygenation: mean sleep peripheral capillary oxygen saturation (SpO_2), nadir sleep SpO_2 (85.8 ± 6.3 % vs 92.6 ± 2.5 %, $p < 0.001$), sleep desaturation where SpO_2 during sleep of less than 90% for ≥ 5 minutes with a nadir of < 85 % (15 versus 0 %, $p < 0.001$) and difference between awake SpO_2 and nadir SpO_2 (9.2 ± 4.6 vs 5.2+ 1.9 %, $p < 0.001$) (Perin et al., 2012). The above study by Perin et al. highlights that sleep efficiency and AHI may be normal in subjects with CF but the more subtle measures of abnormalities during sleep require further development. Milross et al. studied 32 adults with CF using PSG, lung function, respiratory muscle strength and arterial blood gas reports to examine the predictors of sleep disordered breathing (Milross et al., 2001b). These authors concluded that evening PaO_2 significantly contributed to the ability to predict both sleep-related desaturation ($p < 0.001$) and the rise in transcutaneous carbon dioxide from NREM sleep to REM sleep (Milross et al., 2001b).

The vast majority of studies in CF subjects have only included subjects with moderate or severe pulmonary disease from CF (Dobbin et al., 2005), often those patients awaiting lung transplantation, with the studies designed to answer whether non-invasive ventilation offers benefits by reversing respiratory abnormalities during sleep (Dobbin et al., 2004, Katz, 2014, Piper et al., 1992). The subtler changes may suggest the development of an exacerbation rather than frank deterioration in lung function. Hence, the proposed area of research will investigate the relationship between cough, arousals and sleep fragmentation in subjects with CF with a range of lung function.

Overall, there has been a lack of standardisation in defining nocturnal arousals (particularly those due to cough or other respiratory events), making comparisons between studies difficult. Therefore, this research will evaluate the prevalence of sleep disordered breathing in addition to investigating the range of abnormal sleep parameters seen in patients with CF, in particular the presence of cough and other respiratory noises, such as crackles, and the relationship to nocturnal arousals.

1.17 PREVALENCE

The magnitude of the issue of nocturnal desaturation in CF adults was demonstrated in recent studies by Young et al., who showed that more than 25 % of clinically stable CF adults (mean age: 31 years, mean FEV_1 42 % predicted) exhibit nocturnal oxygen desaturation, which was associated with reduced quality of life (Young et al., 2011). A Canadian study of 19 adult CF subjects with severe lung disease (average FEV_1 28 % predicted) found significantly increased arousals from sleep, significantly reduced sleep efficiency, reduced mean arterial oxygen desaturation and worse neurocognitive

function compared with 10 healthy control subjects (Dancey et al., 2002). However, cough and cough related arousals were not reported. Although in their discussion, these authors documented that the sleep technicians reported coughing interfered with sleep in four patients no further analysis was described (Dancey et al., 2002). Cough was proposed as one of the factors that may result in sleep disruption and sleep loss (Dancey et al., 2002).

1.18 PATHOPHYSIOLOGY

Nocturnal cough has the potential to contribute to impaired sleep quality and abnormal sleep architecture by causing arousals. Previous studies have investigated these issues including Stokes et al.; and Francis et al. (Francis et al., 1980, Stokes et al., 1980). In the small study of 9 patients with CF, Stokes et al. demonstrated that in a third of these patients (range FEV_1 17 – 81 % predicted), cough during sleep was associated with sleep disruption (Stokes et al., 1980). In this particular study, episodes of cough (manually observed) during stages 1 and 2 sleep delayed progression to deeper stages of sleep, while protracted cough occasionally halted progression to REM sleep (Stokes et al., 1980). In the study performed by Francis et al., 20 CF patients with severe lung disease (mean age of 18.2 years, mean FEV_1 35.7 % predicted), showed a mean 7.4 % fall in SaO_2 (detailed in their paper as SaO_2, measured by ear oximetry) during REM sleep compared with a 2.0 % fall in the control group (Francis et al., 1980).

Studies have demonstrated that CF patients with severe respiratory disease exhibit marked nocturnal oxygen desaturation and nocturnal carbon dioxide retention when asleep (Milross et al., 2004). Desaturation worsens during sleep due to a combination

of hypoventilation, impaired lung mechanics and ventilation-perfusion mismatching (Milross et al., 2001a).

Intermittent and recurrent nocturnal hypoxia has been a proposed mechanism for the stimulus for the development of pulmonary hypertension in patients with OSA, this may also be seen in CF patients as documented by Fraser et al.(Fraser et al., 1999). Further confirmed by Perin et al., 2012, these authors found that adult CF patients who had sleep hypoxaemia were more predisposed to desaturate at submaximal exercise and to present echocardiographic findings suggesting pulmonary hypertension (Perin et al., 2012, Fraser et al., 1999). However, little research has been performed in adults with CF with mild lung function abnormality.

1.19 Objective Sleep Measurements

Polysomnography

Most studies of sleep in CF subjects have measured in-laboratory PSGs over 1 or 2 nights, examining patients with moderate to severe lung disease secondary to CF. In 19 CF subjects, significantly reduced total sleep time (TST) ($p = 0.048$) and sleep efficiency ($p=0.004$) was seen along with CF subjects demonstrating significant hypoxaemia during sleep (mean oxygen saturation of haemoglobin in arterial blood (SaO_2) 84.4 %), which was associated with reduced sleep efficiency (Dancey et al., 2002). The AHI of CF subjects in the Perin study was normal at 0.3 events per hour, which was not significantly different compared to controls (0.5 events per hour) (Perin et al., 2012). However, in this study there was a small but statistically significant

difference (p = 0.02) between the CF group and normal group for the arousal index (Perin et al., 2012). 14 CF subjects and 8 control subjects underwent exercise testing and overnight sleep studies (Bradley et al., 1999). Interestingly, in comparison to other studies, these authors found no significant differences in sleep efficiency, arousal frequency, or sleep architecture between the CF and control groups (Bradley et al., 1999). However, as expected, oxygen levels during sleep were significantly lower in the CF group (mean FEV_1 of 1.55 Litres) compared with the control group (mean FEV_1 4.01 Litres) (Bradley et al., 1999).

Sonomat

At the time of writing this review, no studies using the Sonomat have been reported in the literature using CF subjects. Hence, this research project will be the first using the Sonomat in CF subjects. We propose a simple non-invasive machine that simply requires the person with CF to sleep on the mat to record a number of variables including sound and movement. This thesis aims to further validate the Sonomat for the characterisation of respiratory sounds which may be important for managing people with CF-related lung disease.

1.20 SUBJECTIVE MEASUREMENTS

Epworth Sleepiness Scale (ESS)

The ESS is a commonly used measurement of daytime sleepiness (Johns, 1991). Subjects are asked to rate on a scale of 0-3 how likely they would be to doze off or fall

asleep in eight different situations (Johns, 1991). The raw numbers are summed together to give a score between 0 and 24. It has been well validated in the OSA population but has also been used in studies of CF subjects. In the study by Jankelowitz et al., the mean ESS scores for the CF subjects were higher but not statistically significant than in the control subjects (6.75 ± 3.32 vs 5.72 ± 3.63, $p = 0.39$), however, the value was still considered normal (ESS < 10) (Jankelowitz et al., 2005). In another study by Dancey et al., again ESS was within normal limits (ESS 7.3 ± 4.4) (Dancey et al., 2002).

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-reported questionnaire that measures the subjects' recollection of sleep quality over the previous four weeks. The PSQI consists of 19 questions. A global PSQI score of greater than 5 indicates that a subject is a "poor sleeper" (Buysse et al., 1989). The PSQI has been used previously in studies of CF subjects including a study by Jankelowitz et al., investigating sleep quality and sleep disruptions in CF patients (Jankelowitz et al., 2005). These authors found that the PSQI score was significantly higher in CF subjects (6.45 ± 3.31, $p = 0.04$) than in controls (Jankelowitz et al., 2005). In a study of 51 clinically stable adult CF patients and 25 age-matched controls, CF patients had significantly higher ESS, PSQI scores as well as a higher arousal index than the controls ($p < 0.05$) (Perin et al., 2012).

CF Quality of Life (QoL)

QoL in adults with CF has been previously studied by a number of authors. More recently due to the emerging therapies targeting certain CF gene mutations, there has been interest in assessing changes in quality of life following commencement of these novel drugs. Hence, QoL questionnaires are being utilised to assess important secondary endpoints of clinical trials that are not always demonstrated by change in spirometric parameters or exercise capacity.

There are currently a number of questionnaires that have been validated to assess quality of life including depression and anxiety in chronic respiratory diseases. The most utilised questionnaires for chronic respiratory patients include: the St George Respiratory Questionnaire (SGRQ) (Jones et al., 1991) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). In particular for CF patients, two main questionnaires were developed: the Cystic Fibrosis Questionnaire (CFQ) English version (Quittner et al., 2000), then the CFQ-Revised (Quittner et al., 2005) and the CF QoL questionnaire (Gee et al., 2000). The CFQ-R has been the primary questionnaire utilised as a measure of secondary endpoints in therapeutic drug trials. The CFQ-R and CF QoL are further discussed below.

The St George Respiratory Questionnaire (SGRQ) was initially designed to measure the impact of overall well-being in patients with obstructive airways disease including those patients with COPD (Jones et al., 1992, Harper et al., 1997), asthma (Jones et al., 1991, Quirk et al., 1991) and bronchiectasis (Wilson et al., 1997). In the SGRQ, there are 50 items with 76 weighted responses divided into 2 parts with 3 components

including symptoms, activity and impacts components. The weights provide an estimate of the distress associated with the symptom or state described in each item. Scores ranging from 0 to 100 are calculated for each component, as well as a total score which summarises the response to all items (Jones et al., 1991). A score of zero indicates no impairment of quality of life (Jones et al., 1991). A previous multi-centre study showed significant correlations between total score and presence of cough, sputum and wheeze in 141 subjects with long-standing airflow limitation (r^2 = 0.11, 0.06 and 0.25, respectively; $p < 0.0001$, $p = 0.002$ and $p < 0.0001$, respectively) (Jones et al., 1992). In particular, the SGRQ symptom score was significantly higher indicating worse health in patients with daily cough and sputum production (Jones et al., 1992). Correlations found between SGRQ scores and a range of measures appeared to be appropriate to the section of the SGRQ under study. However, the major limitation of this questionnaire is that it has not been validated in the CF population. Therefore, a need was identified to establish a QoL questionnaire that captured different aspects of QoL in CF patients, hence the CFQ was created.

Other scales have measured different items, for example, the Medical Research Council (MRC) respiratory symptoms questionnaire and MRC dyspnoea scale. The MRC dyspnoea scale and 6 minute walking distance were closely related to SGRQ Activity score ($p = 0.0001$, $p = 0.0052$, respectively) but not to the SGRQ Symptom score ($p = 0.16$, $p = 0.53$, respectively) in the above study of patients with long-standing airflow limitation (Jones et al., 1992). Anxiety and depression scores correlated best with the SGRQ Impact section ($r^2 = 0.38$, $r^2 = 0.39$, respectively) (Jones et al., 1992). The dominant factors influencing the total SGRQ score were found to be wheeze, dyspnoea and anxiety (Jones et al., 1992). The SGRQ was subsequently translated from British

English to American English (SGRQ-A) and was modified by altering the time of symptom reporting from 1 year to 1 month. The total scores based on the 1-year and 1-month symptom reports correlated with FEV_1, MRC dyspnoea scale and 6MWT distance ($p \leq 0.01$) but not the FEV_1 % predicted (Barr et al., 2000).

Zigmond and Snaith, 1983, developed a self-assessment scale used to detect states of depression and anxiety in the setting of a hospital medical outpatient clinic called the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS contains 7 items in the two areas of anxiety and depression with each item scored between 0 and 3. The assessment for each patient takes about 20 minutes. The total score for anxiety and depression is calculated separately with a score of 0 - 7 indicating normal emotions, 8-10 indicating a borderline abnormal emotional disorder and a score of 11 - 21 demonstrating an abnormal emotional disorder (Zigmond and Snaith, 1983). The HADS has not been widely used in the CF population and has not been validated in this population so was not used during the current study.

Cystic Fibrosis Quality of Life (CF QoL) Questionnaire

Gee et al., 2000 developed a disease specific health related QoL measurement, the Cystic Fibrosis Quality of Life (CF QoL) (Gee et al., 2000). They identified a need to measure the impact of CF on daily functioning and interviewed patients, specialist medical and allied health staff as well as reviewed the literature and examined other QoL measures to identify specific areas of concern to adults and adolescents with CF. The developed validated questionnaire can be used: as an outcome measure in clinical trials; to assess the impact of disease progression on patient's well-being; and, for

monitoring individual patients. The CF QoL questionnaire is a fully validated disease specific measurement consisting of 52 items in total which covers the 8 domains of: physical functioning; social functioning; treatment issues and chest symptoms; emotional functioning, concerns for the future, interpersonal relationships; body image; and career concerns (Gee et al., 2000). All items are scored from 1 to 6 and then scaled to produce a score of between 0 and 100 for each section above. A transformed score indicates the value that has been achieved out of a maximum of 100 with 100 indicating the most positive QoL levels possible. As this is a validated disease specific questionnaire it was thought its use in the current study would complement the results of the CFQ-R measurement currently under widespread use in clinical trials. The CF QoL measure can also be used to assess patient's well-being longitudinally and Gee et al., 2005 described data from routine clinical use that would suggest a change of 5 points on the CF QoL scales can indicate a small, meaningful change as perceived by the patient (Gee et al., 2005).

Cystic Fibrosis Questionnaire (CFQ) and Cystic Fibrosis Questionnaire-Revised (CFQ-R)

Originally, the CFQ was designed by the French group starting in 1995 led by Bernadette Henry and Peirre Aussage and was then translated into the English version by Quittner et al. (Henry et al., 2003, Quittner et al., 2000). Later it was revised by Quittner et al. and the results were published in 2005 as the CFQ-revised version (Quittner et al., 2005). To be discussed in Chapter 2 – Methods, the CFQ-R questionnaire was used in this study as it has been well validated in the CF population. Briefly, the CFQ-R is a disease-specific questionnaire that measures health related

quality of life for patients older than 14 years (Quittner et al., 2005). This questionnaire consists of 44 items on 12 generic and disease-specific scales. It encompasses general domains of quality of life: physical functioning, role functioning, vitality, health perceptions, emotional functioning and social functioning, as well as domains specific to CF: body image, eating disturbances, treatment burden, and respiratory and digestive symptoms (Quittner et al., 2005).

Of note, the CFQ-R has only one question pertaining to sleep or night time symptoms: "Have you woken up during the night because you were coughing?" (Quittner et al., 2005). CF patients may experience sleep disturbances due to a number of factors including awakening due to cough, pain, medications or sleep disordered breathing. In turn, these sleep disturbances can impact on the quality of life in CF patients.

Although the generic and disease specific questionnaires are useful to investigate various quality of life domains, sleep is not highly featured in these questionnaires. For example, in both the SGRQ and CFQ-R, there is only one item that asks about sleep disturbance as a result of cough and breathlessness (Jones et al., 1991, Quittner et al., 2005).

Studies of sleep disturbance in CF patients have been performed but few studies have looked at the correlation of these sleep disturbances and QoL. Hence, upon review of the current literature, the Pittsburgh Sleep Quality Index (PSQI) was found to be the most robust and has been previously used to assess sleep quality in CF patients (Buysse et al., 1989). The details of the PSQI can be found in Chapter 2 - Methods.

In clinically stable adults with CF, impaired sleep quality measured by the PSQI was related to reduced disease-specific QoL in CF (Bouka et al., 2012). In this study, higher PSQI scores significantly correlated with lower CFQ-R scores for specific domains of vitality, emotional functioning, social, role, eating disturbance and digestive symptoms ($p<0.05$) (Bouka et al., 2012). These results are in keeping with the knowledge that poor sleep quality impacts on an individual's quality of life. Although the PSQI was able to show correlations with CFQ-R, the Epworth Sleepiness Scale did not show these correlations except in the vitality domain (Bouka et al., 2012). Higher scores on the PSQI correlated with lower scores on the domains looking at mental health (vitality, emotional functioning, social and role). Hence, anxiety and depression may be related to reduced quality of sleep in CF patients. Other factors including nocturnal hypoxaemia, disorders of breathing during sleep and gastrointestinal issues can all impact negatively on sleep and sleep quality. The PSQI is the only questionnaire that attempts to address some of these issues (Buysse et al., 1989).

Of the questionnaires evaluated for review above, the most rigorously tested and the most applicable for our CF population, included the PSQI, CF QoL and the CFQ-R. These questionnaires were used in Chapter 6 – Sleep Quality and Quality of Life in Adults with CF to examine the relevant issues (QoL as well as sleep quality) for adults with CF with a range of lung function.

SUMMARY

Cystic fibrosis (CF) is a genetic disease which is associated with lung disease secondary to recurrent respiratory infections caused by impairments of mucociliary clearance. These infections can result in progressive lung scarring, respiratory failure and ultimately death. Respiratory sounds including cough and crackles may indicate sputum retention in adults with CF. Use of non-invasive methods to measure respiratory sounds and events will be trialled during sleep to establish if there are changes which occur during sleep in adults with CF. Evaluation of the quality of life and sleep quality in patients with CF will also be studied in this thesis to add to the knowledge base of the issues that affect these patients.

This PhD thesis will examine a number of areas related to the recording and characterisation of respiratory sounds and sleep disordered breathing that occurs in adults with CF. The following chapters will outline the results of each of the projects undertaken to examine the above areas of interest. Chapter 2 will outline the Methods undertaken for each of the projects. Respiratory sounds will be discussed using the results from analyses of the Sonomat in Chapter 3. The results of overnight sleep studies using both the in-laboratory PSG and Sonomat will be examined in Chapters 4 and 5. Quality of life in adults with CF will be reported in Chapter 6. In Chapter 7, conclusions from the thesis will be detailed.

CHAPTER 2: METHODS

2.1 INTRODUCTION

All data in this thesis were obtained from adults (aged 18 – 70 years) who gave consent for the acquisition and analyses of data. There were four main areas of measurements in this thesis, namely: 1. questionnaires measuring the quality of life in adults with cystic fibrosis (CF) as well as the quality of sleep; 2. abnormalities of sleep structure in adults with CF; 3. identification of respiratory sounds using alternative and novel techniques; 4. respiratory sounds recorded at night. The methods involved in these areas are discussed below.

2.2 SUBJECTS

Adults with CF were recruited from the CF Service at Westmead Hospital, Sydney. The diagnosis of CF had been confirmed on genetic testing and / or elevated sweat chloride levels (> 60 mEq/L). Patients attending the adult CF service at Westmead Hospital (aged >18 years) between 1st January 2013 until 30th November 2016 were approached and offered the opportunity to participate in any or all of the projects.

The protocols were all approved by the Westmead Hospital Human Research Ethics Committee (HREC2012/12/4.9(3627) AU RED HREC/12/WMEAD/427. Written informed consent was obtained for all subjects.

2.3 ANTHROPOMETRIC DATA

Data recorded included: a) CFTR genotype; b) age; c) gender; d) standard anthropometric data consisting of: weight, height and calculation of body mass index (BMI).

2.4 LUNG FUNCTION

Lung function was recorded using the Vitalograph® (Vitalograph, Lenexa, KS, United States). Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society criteria (Miller et al., 2005). Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were recorded. Predicted spirometric parameters were derived using reference values from Hankinson et al., 1999 (Hankinson et al., 1999). Disease severity was classified using the equations for percentage predicted of FEV_1 and divided into: mild ($FEV_1 \geq 70$ % predicted), moderate (FEV_1 60-69 % predicted), moderately severe (FEV_1 50-59 % predicted), severe (FEV_1 35-49 % predicted) and very severe ($FEV_1 < 35$ % predicted) categories (Pelligrino et al., 2005).

2.5 QUESTIONNAIRES

Participants completed four questionnaires: i). Cystic Fibrosis Questionnaire – Revised (CFQ-R) Appendix A (Quittner et al., 2005); ii). CF Quality of Life (CF QoL) questionnaire Appendix B (Gee et al., 2000); iii). Pittsburgh Sleep Quality Index

(PSQI), Appendix C (Buysse et al., 1989); iv). Epworth Sleepiness Scale (ESS), Appendix D (Johns, 1991).

i). Cystic Fibrosis Questionnaire – Revised (CFQ-R) (Quittner et al., 2005). The CFQ-R is a disease-specific questionnaire that measures health related quality of life over the preceding 2 weeks for people with CF older than 14 years (Quittner et al., 2005). This questionnaire consists of 44 items on 12 generic and disease-specific scales. It encompasses general domains of quality of life: physical functioning, role functioning, vitality, health perceptions, emotional functioning and social functioning; as well as domains specific to CF: body image, eating disturbances, treatment burden, and respiratory and digestive symptoms (Quittner et al., 2005). Each item included ratings of frequency or difficulty on a 4-point scale (where 1 = always, 2 = often, 3 = sometimes, 4 = never; or 1 = very true, 2 = somewhat true, 3 = somewhat false, 4 = very false; see Table 2.1). Scores are then standardised on a 0 to 100-point scale, with higher scores representing better quality of life for each particular domain. In the pre-transplant group of participants who underwent two separate sleep studies longitudinally, assessment of the differences between the two-time points was based on previous work performed by Quittner et al. (Quittner et al., 2009). These authors reported the minimal clinically importance difference score was 4.0 (for stable subjects) whilst a change of 8.5 points (for subjects with a current exacerbation) was used to define improvement after a 28-day course of inhaled tobramycin (Quittner et al., 2009).

Table 2.1. Cystic Fibrosis Questionnaire – Revised (CFQ-R) Scoring

Answer		**Score**
Very true	Always	1
Somewhat true	Often	2
Somewhat false	Sometimes	3
Very false	Never	4

4-point scale used for scoring in CFQ-R.

CFQ-R: Cystic Fibrosis Questionnaire – Revised.

ii). CF Quality of Life (CF QoL) questionnaire (Gee et al., 2000). This is a self-administered questionnaire developed by Gee et al. (2000) (Gee et al., 2000), which measures the self-described quality of life over the previous 2 weeks in several domains. This questionnaire contains 52 items in total which covers the 8 domains of: physical functioning; social functioning; treatment issues and chest symptoms; emotional functioning; concerns for the future; interpersonal relationships; body image; and career concerns. All items are scored from 1 to 6 (see Table 2.2) and then scaled to produce a transformed score of between 0 and 100 for each section. A transformed score indicates the value that has been achieved out of a maximum of 100 with 100 indicating the most positive QoL levels possible.

Table 2.2. Cystic Fibrosis – Quality of Life (CF QoL) Scoring

For Sections 1 to 4 answers	For Sections 5 to 8 answers	Score
All of the time	Strongly agree	1
Most of the time	Agree	2
Good bit of the time	Slightly agree	3
Sometimes	Slightly disagree	4
Occasionally	Disagree	5
Never	Strongly disagree	6

Scoring of CF-QOL, using a 6-point scale. CF-QOL: Cystic Fibrosis Quality of Life Questionnaire.

iii.) Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-completed questionnaire that records subjective sleep quality over the previous four weeks. The PSQI consists of 19 questions. Seven domains of sleep are covered: duration of sleep; sleep disturbance; sleep latency; daytime dysfunction due to sleepiness; sleep efficiency; overall subjective sleep quality; requirement of medications to sleep. The range of values for each scored domain is 0 to 3, see Table 2.3. For questions 1 to 4, each question is scored according to the PSQI scoring system to calculate the transformed score between 0 and 4 (see Appendix A). In the event that a range is given for an answer (eg 30 to 60 minutes is written as the answer to question 2, "minutes to fall asleep"), the average of the two values was calculated and then entered (eg 45 minutes in the above example). In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven domain scores are then added to yield one "global" score, with a range of 0 to 21 points, "0" indicating no

difficulty and "21" indicating severe difficulties in all areas. A global PSQI score of greater than 5 indicates that a subject is a "poor sleeper" (Buysse et al., 1989).

Table 2.3. Pittsburgh Sleep Quality Index (PSQI) Scoring

Answer	**Score**
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three of more times per week	3

Scoring on a 4-point scale for PSQI.

iv). Those subjects who underwent an overnight diagnostic sleep study also completed the Epworth Sleepiness Scale (ESS) on the night of their study Appendix D (Johns, 1991). The ESS is a commonly used measurement of daytime sleepiness (Johns, 1991). It is a self-administered questionnaire and the subjects are asked to rate on a scale of 0 to 3 how likely they would be to doze off or fall asleep in eight different situations (Johns, 1991), where 0 = would never doze, 1 = slight chance of dozing, 2 = moderate change of dozing, 3 = high chance of dozing (see Table 2.4). The situations included: sitting and reading; watching television; sitting, inactive in a public place; as a passenger in a car for an hour without a break; lying down to rest in the afternoon when circumstances permit; sitting and talking to someone; sitting quietly after a lunch without alcohol; in a car, while stopped for a few minutes in the traffic. A distinction was made between dozing off and simply feeling tired. The raw numbers were added to give a score between 0 and 24. A raw score of 10 or greater in the general population was considered to suggest increased daytime somnolence.

Table 2.4. Epworth Sleepiness Scale (ESS) Scoring

Chance of dozing	Score
Would never doze	0
Slight chance of dozing	1
Moderate chance of dozing	2
High chance of dozing	3

For each situation, subjects were asked to score chance of dozing on a 4-point scale (0 to 3). Total score out of 24.

2.6 POLYSOMNOGRAPHY

Standard overnight in-laboratory polysomnographic (PSG) recordings were performed using a computerised acquisition system (Compumedics E-series, Compumedics, Abbotsford, Victoria, Australia). The PSG recorded the following signals: electro-encephalogram (EEG), electro-oculogram (EOG), submental electro-myogram (EMG), electro-cardiogram (ECG), thoraco-abdominal excursion (respiratory induction plethysmography), nasal flow (pressure transducer), oro-nasal flow (thermistor), snoring sounds (calibrated room sound level meter; Rion NL-20, NL-31; Rion Co. Ltd, Tokyo, Japan), pulse oximetry (SpO_2; Biox 3700s; Ohmeda, Boulder, CO, USA), leg movements, and body position.

Polysomnography Scoring Criteria

All PSG studies were scored according to the American Academy of Sleep Medicine (AASM) 2007 guidelines for scoring sleep stages, arousals, and respiratory events with

the alternate (Type B) hypopnoea criteria used (Iber et al., 2007). The studies were all scored using the 2007 AASM guidelines in use prior to the adoption of the revised guidelines published by Berry et al. in 2012 (Berry et al., 2012).

Sleep Stages

Stage W (wake) was scored when more than 50 % of the epoch had alpha rhythm over the occipital region. Stage N1 non-REM sleep (NREM) sleep was scored when the alpha rhythm was attenuated and replaced by low amplitude, mixed frequency activity for more than 50 % of the epoch. In subjects who did not generate alpha rhythm, scoring stage N1 commenced with the earliest of any of the following phenomena: activity in the range of 4-7 Hz with slowing of background frequencies by ≥ 1 Hz from those of stage W; Vertex sharp waves; or Slow eye movements. Stage N2 NREM sleep occurred when one or both of the following occurred during the first half of that epoch or the last half of the previous epoch: one or more K complexes not associated with arousals; or one or more trains of sleep spindles. Stage N3 NREM sleep was scored when 20 % or more of an epoch consisted of slow wave activity. Stage R (Rapid eye movements (REM) sleep) was scored when all of the following occurred within that epoch: low amplitude, mixed frequency EEG, low chin EMG tone and REM (Iber et al., 2007).

Scoring of events

Total sleep time in the PSG included sleep during all stages of sleep. By convention, there had to be 10 seconds of sleep before an arousal, defined as an abrupt change in

EEG signal to higher frequencies lasting from 3 to 15 seconds, could be scored. If these changes persisted for more than 15 seconds, the epoch was then scored as awake.

An apnoea was defined as a reduction in amplitude of airflow (both nasal pressure and flow thermistor) to less than 10 % of baseline for at least 10 seconds. A central apnoea was defined by the absence of respiratory effort on thoracic and abdominal inductive plethysmography signals. An obstructive apnoea was defined as an apnoea characterised by continuation or an increase of respiratory effort on thoracic or abdominal inductive plethysmography or diaphragmatic EMG. Hypopnoeas were scored when the following criteria were fulfilled: 1. A clear decrease (≥ 30 %) from baseline in the amplitude of a breathing signal (nasal pressure or inductive plethysmography) during sleep, with baseline defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern); 2. This decrease in breathing was associated with oxygen desaturation of ≥ 3 % or an EEG arousal; 3. The event lasted longer than 10 seconds, and at least 90 % of the event's duration must have met the amplitude reduction criteria.

Apnoea-Hypopnoea Index (AHI) was defined as the number of apnoeas and hypopnoeas per hour of sleep. Respiratory disturbance index (RDI) was the total number of apnoeas, hypopnoeas and respiratory effort related arousals (RERAs) per hour of sleep. Periodic limb movements of sleep were scored when at least 4 consecutive leg movements occurred, providing each individual leg movement had a

duration of between 0.5 and 10 seconds. Each leg movement was separated by an interval of between 4 and 90 seconds. Sleep efficiency was calculated by dividing the total sleep time by total time from sleep onset to awakening next morning. A spontaneous arousal was defined as an arousal with no detectable cause. A respiratory arousal was defined as an arousal caused by a hypopnoea or apnoea. A RERA was defined as flattening of the nasal pressure waveform last for 10 seconds or longer, and leading to an arousal, but not reaching criteria for hypopnoea. Arousal index was defined as the total of spontaneous, respiratory and leg movement arousals per hour of sleep. Oxygen desaturation index (ODI) was defined as the number of times per hour that the SpO_2 reduced by at least 3% from baseline.

2.7 SONOMAT

The Sonomat device was developed by Sonomedical Pty Ltd (Balmain, NSW, Australia). The mattress was made from a thin piece of foam (Dunlop Foams, Dandenong, Victoria, Australia) with dimensions of 650 mm (width) x 1780 mm (length) x 40 mm (thickness) to sit on top of a regular single sized mattress. The foam was enclosed with StaphChek (Herculite, Emigsville, PA, USA), which is a protective thermoplastic fabric commonly used in healthcare environments that can be cleaned between subjects. The mattress can be folded for ease of transport with a total weight of 6 kilograms. Four identical sensors were embedded into the foam mattress and these contained a polyvinylidine fluoride (PVDF) foam that generated a voltage when deformed, by sounds and movements. Sounds were recorded using these 4 sensors as well an additional two room microphones embedded in the foam mattress. The Sonomat setup included an in-built microprocessor to analyse the outputs of the PVDF foam and

sound sensors recording them on a standard secure digital (SD) card. The microprocessor mattress was connected to an earthed power source. The mattress was placed directly on top of the subject's bed mattress, covered with a standard sheet. The subject lay on the Sonomat with no physical attachments or wires impeding sleep.

The Sonomat recording was started manually via a button pressed by a sleep technician in the Sleep Lab. At the time of awakening in the morning, the Sonomat was turned off using the same process as above by a sleep technician. Data were stored on a SD card (SanDisk, Milpitas, CA) within the Sonomat in a proprietary file format. At the end of the study, the SD card was removed and the files manually transferred to a computer for further analysis.

Acoustic signals were recorded at a sampling frequency of 4000 Hz and movement signals were recorded at a sampling frequency of 250 Hz. The two room microphones were each capable of detecting audible room sounds in the range 20 Hz to 2000 Hz. Software developed to review the Sonomat recordings (Sonomat Replay) allowed visual interpretation of signals, audible replay of the recorded sounds and the manual scoring of specific physiological events.

Sonomat Scoring Criteria

Using the Sonomat, the definition of sleep onset could not include the EEG criteria listed above for the PSG. Sleep onset was defined at the last series of frequent body

movements which followed the subject lying down with the intention to sleep. Awakening was defined when frequent body movements persisted or sounds (such as talking) indicated the subject was awake. Body movements were considered to be indicative of wake similar to actigraphy, a well-accepted method of quantifying sleep from movement-based signals. The total duration of "wake time" (body movements) was removed from the total recording time (TRT) to calculate the "quiescent duration" (Qd). This Qd duration (minutes), containing all periods of postural immobility, was used as an estimate of total sleep time (TST).

Respiratory sounds taken from audio sensors and room microphones in the Sonomat were analysed visually and if necessary, clarified using manual audio replay of sounds. Furthermore, the sound was analysed using WaveSurfer (WaveSurfer 1.8.8p4 - 1112300908. Copyright © 2000-2011 Jonas Beskow and Kare Sjolander), a software program that produces spectrograms allowing a visual representation of sound. Interactive sound analysis software was also used to analyse cough sounds (Mills et al., 2018).

Respiratory sounds were scored throughout the night. These sounds included: snores, cough, crackles and wheezes. All respiratory sounds could be identified visually and classification could be confirmed with auditory replay.

Snores were characterised by periodic components and harmonics in the breath sounds with fundamental frequency peaks from 20-30 Hz up to approximately 250-300 Hz

were scored as snores within Sonomat recordings.

Cough sounds were differentiated from breath sounds as sounds that contained an initial wide distribution of sound frequencies between 50 and 2000 Hz of short duration and high sound intensity which then tapered off over the next few seconds. Cough sounds were further classified into a single cough or multiple coughs and were confirmed on audio replay. Total cough time was the total time of cough sounds analysed on the study. Cough time per hour was generated by dividing the total cough time by the Qd.

Crackles were visually identified when rapid bursts of high amplitude "popping" sounds were present. When more than 1 second of a breath contained multiple popping sounds, across inspiration and/or expiration, the breath was scored as containing crackles. Again, crackle time per hour was generated by dividing the total time of crackle sounds by the Qd.

Finally, wheezes were identified by visual analysis where there was a predominant "musical" frequency of ≥ 400 Hz at very high intensity and duration of more than 500ms. Wheeze time was calculated based on the number of seconds the breath sounds contained wheeze sounds. Wheeze time per hour was generated by dividing total wheeze time by the Qd.

Sonomat scoring criteria of respiratory events were developed to be similar to PSG

AASM scoring guidelines (Iber et al., 2007). However, the Sonomat used the breath sounds signal as a measure of airflow. To ensure scoring consistency, the minimum duration of a respiratory event was defined as at least 10 seconds. Respiratory events scored using the Sonomat included: hypopnoeas (reduction of breathing movements from baseline by ≥ 30 %) and apnoeas (complete cessation of breath sounds). An obstructive apnoea was scored when the absence of breath sounds was associated with continued breathing movements. A central apnoea was scored when the absence of breath sounds was associated with the absence of breathing movements. The Apnoea-Hypopnoea Index from the Sonomat studies (AHI MAT) was generated by dividing the number of respiratory events by the Qd. It should be noted that the Sonomat is not able to score RERAs (which were based on flattening of the nasal flow data tracings and EEG arousals in PSG) and the PSG was not able to identify coughs, crackles or wheezes.

2.8 Statistical Analyses

Statistical and graphical analyses were performed using SPPS v.22 (SPSS Inc., IL, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). Normally distributed data were presented as mean ± standard deviation (SD), and non-normally distributed data were presented as median and interquartile range (IQR). Further details regarding specific statistical analyses relevant to each study will be discussed in each chapter.

CHAPTER 3: RESPIRATORY SOUNDS

3.1 INTRODUCTION

The identification of respiratory sounds has been an essential part of the physical examination performed by doctors for many years. Differences in the pulmonary sounds can lead the physician to diagnose a variety of pulmonary and cardiac conditions, but often the classification is very subjective, dependent on the physician involved.

3.1.1 Classification of Respiratory Sounds

The European Respiratory Society (ERS) Task Force on Respiratory Sounds established a project, entitled Computerized Respiratory Sound Analysis (CORSA), to provide consensus through standardisation of respiratory sounds nomenclature (Pasterkamp et al., 2016). They presented their findings in 2016 in the European Respiratory Journal (Pasterkamp et al., 2016). Using a standardised set up of a professional stethoscope attached to a small microphone and video camera, data were acquired and recorded. A reference collection of 20 recordings was used and described by expert members of the Task Force (Pasterkamp et al., 2016). Further to the classification used by CORSA, a modification was recommended by the ERS Task Force to use “normal (basic) sounds” instead of “breath sounds” (Pasterkamp et al., 2016). Also, these authors recommended the term “vesicular sounds” should be replaced by “normal” or “basic” lung sounds (Pasterkamp et al., 2016).

3.1.2 Normal Lung Sounds

The breathing sound heard on the chest of a healthy person is called a normal lung sound, previously known as a breath sound or vesicular sound. It is a noise that peaks in frequency below 100 Hz, where it is mixed with and difficult to distinguish from muscle and cardiovascular sounds (Gavriely et al., 1981). The characteristics of normal lung sounds heard over the chest wall are the result of the nature of the sound generator and the distortion of the sound upon transmission to the location of detection. For normal lung sounds, the power of the signal decreased exponentially as frequency increased as detailed in a study of 10 healthy subjects by Gavriely et al. (Gavriely et al., 1981). In the review by Pasterkamp et al., the normal lung sound spectrum is devoid of discrete peaks and is not musical (Pasterkamp et al., 1997).

Body size also affects respiratory sounds. Pasterkamp et al. reported after studying 9 infants compared with 20 older children and adults that the main difference of lung sounds in infants compared with older children and adults was in the reduction in power below 250 Hz, whereas sound attenuation above 300 Hz was similar (Pasterkamp et al., 1996a). The different resonance behaviour of a small thorax and small airways or less contribution of low frequency muscle noise may explain the difference of normal lung sounds in young children (Pasterkamp et al., 1996a).

3.1.3 Normal Tracheal Sounds

The tracheal sound signal is loud covering a wider range of frequencies than lung sounds at the chest wall, with distinct inspiratory and expiratory phases and a close relation to airflow (Gavriely and Cugell, 1996). Respiratory and Sleep Physicians are interested in tracheal sounds as indicators of upper airway flow obstruction and as the source for qualitative and potentially quantitative assessments of airflow. The generation of tracheal sounds is primarily related to turbulent air flow in upper airways, including in the pharynx, glottis, and subglottic regions. Flow turbulence and jet formation at the glottis cause pressure fluctuations within the airway lumen. Sound pressure waves within the airway gas, and airway wall motion are likely contributing to the vibrations that reach the neck surface and are recorded as tracheal sounds (Pasterkamp et al., 1997).

Tracheal sounds have been characterised as broad spectrum sound, covering a frequency range from less than 100 Hz to more than 1500 Hz, with a sharp reduction in power above a cut off frequency of approximately 800 Hz (Gavriely et al., 1981). The spectra of tracheal sounds exhibit peaks and troughs that are related to airway dimensions and dependent on gas density, indicating their origin from resonance within the upper airways. In another study by Pasterkamp, Schafer et al., the spectral shape of tracheal sounds is highly variable between subjects but quite reproducible within the same person, reflecting the strong influence of individual airway anatomy (Pasterkamp et al., 1996b). Soufflet et al., looked at different methods of evaluating instantaneous flow from tracheal sounds and found differences in reference curves observed among

subjects are likely explained by the different airway morphological features of subjects (Soufflet et al., 1990).

3.1.4 Bronchial breathing

Bronchial breathing has been characterised by soft, non-musical sounds, heard on both phases of the respiratory cycle (can mimic tracheal sounds). These sounds indicate patent airway surrounded by consolidation lung tissues or fibrosis (Bohadana et al., 2014).

3.1.5 Adventitial Sounds

A variety of pulmonary sounds have been described including crackles (rales, crepitations, discontinuous adventitial sounds); wheezes (rhonchi, continuous adventitial sounds); coughs; squawks or squeaks. Note, that coughs are produced by the upper airway but will be discussed in this section.

More than 40 years ago, Murphy et al. proposed a technique to characterise pulmonary sounds objectively using time-amplitude plots to provide reproducible visual displays of the different features of pulmonary sounds (Murphy et al., 1977). These authors proposed that time-expansion wave-form analysis of pulmonary sounds provides a scientific and objective method for differentiating the various lung sounds that could aid in the diagnosis of a variety of pulmonary and cardiac conditions (Murphy et al., 1977).

Spectrograms give a visual representation of the spectral information of lung sounds showing frequency and amplitude against time. The x-axis corresponds to time and the y-axis corresponds to frequency. The spectrogram displays the timing in the breathing cycle at which a particular frequency / amplitude combination occurs. Coloured spectrograms highlight significant amplitude features (z-axis). Intensity of the sound at a particular instance is represented by the different colours of the spectrogram, as shown below in Figure 3.1, reproduced from Reichert et al. (Reichert et al., 2008).

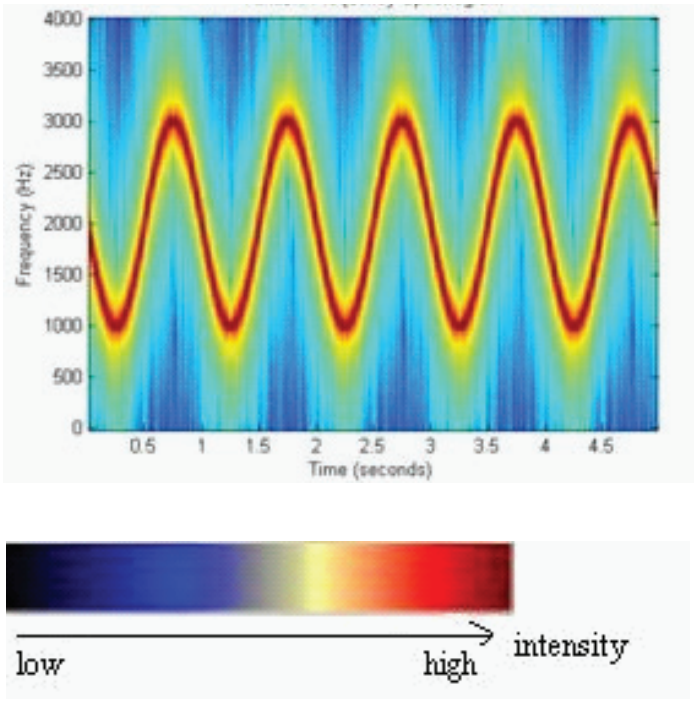

Figure 3.1 Example of a Spectrogram. Reproduced from Reichert et al. 2008 (Reichert et al., 2008)

Time expanded waveform analysis (TEWA) is a technique that assists in distinguishing between the different patterns of lung sounds by presenting the details of the acoustic signal with increased resolution. This is accomplished by zooming in on the time or x-axis of the waveform. Sahgal demonstrated some examples of time domain plots of

lung sounds in both time unexpanded and time expanded modes (Sahgal, 2011). For example, normal tracheal lung sounds have an irregular shape without repetitive patterns on the time-domain plots. Wheeze and rhonchi have a periodic waveform, which is either sinusoidal or more complex. Crackles show a sudden short deflection followed by deflections with greater amplitude (Figure 3.2, reproduced from Sahgal (Sahgal, 2011).

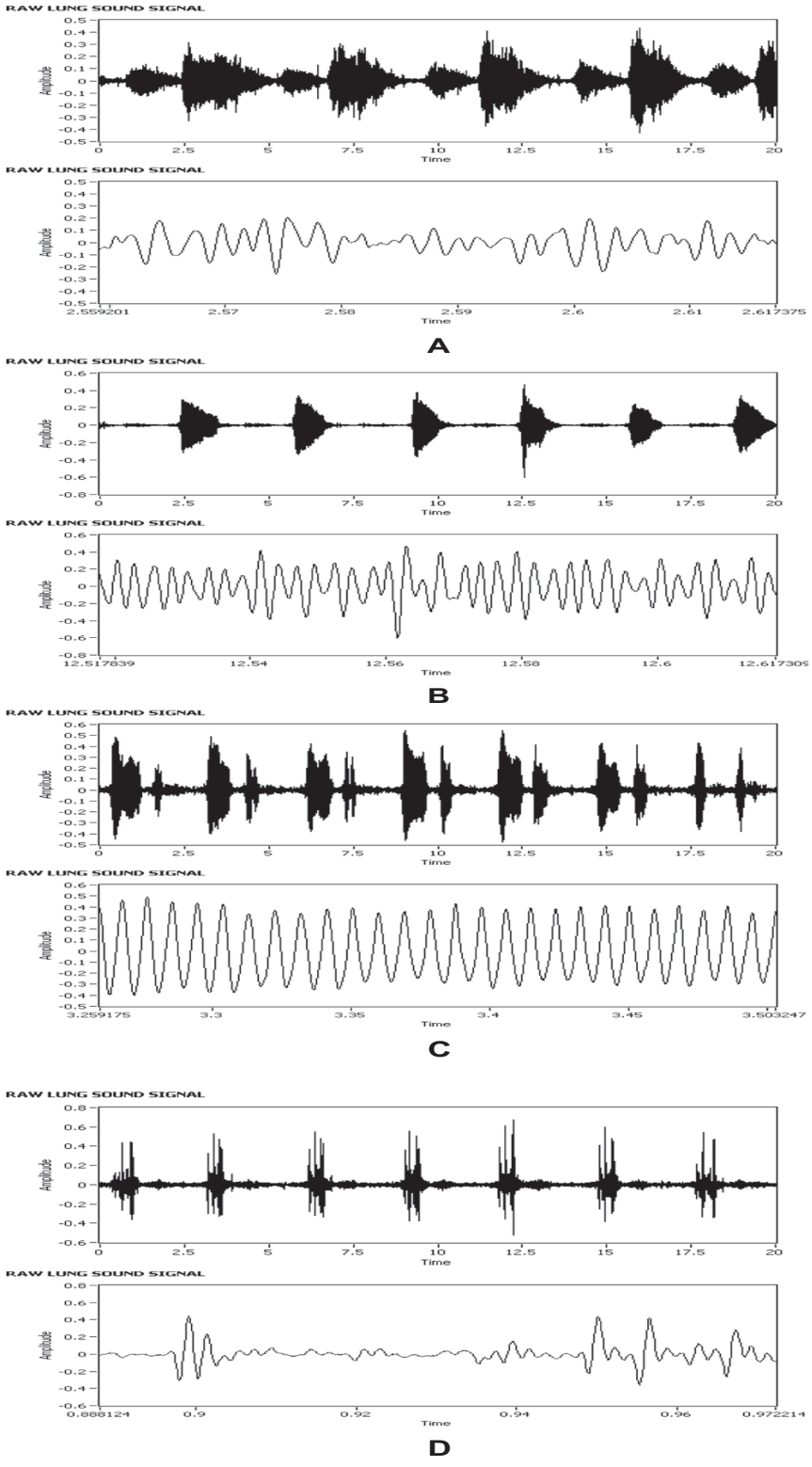

Figure 3.2 Time (seconds) domain plots of the amplitudes of lung sounds. Seen in both the time unexpanded (top panels) and time expanded (bottom panels) modes. A) normal tracheal lung sounds; B) wheeze; C) rhonchi; D) crackle; (Sahgal, 2011).

Wheezes

In respiratory medicine, wheeze is perhaps the most widely used acoustic term. Wheezes are thought to be musical in character and are continuous sounds characterised mainly by their pitch harmonics and duration. They are typically last longer than 80 to 100 milliseconds, with their fundamental frequency and harmonics greater than 100 Hz. Their frequency range extends from less than 100 Hz to more than 1 kHz and higher frequencies may be measured inside the airways (Akasaka et al., 1975). In 1977, the ATS proposed that wheezes may not necessarily extend more than 250 ms, but will be typically longer than 80 to 100 ms (Cugell et al., 1977).

Wheezes usually identify the presence of an obstructive pathology, for example, asthma. Sahgal demonstrated the frequency spectrum of wheeze contained a dominant frequency of 400 Hz (Sahgal, 2011). Rhonchi is a term to refer to a low-pitched wheeze with a duration of more than 100 milliseconds and frequency of less than 300 Hz. Furthermore, wheezes are mainly a sound production phenomenon, whereas breath sounds over a lobar pneumonia are mostly due to changes in the transmission function of the affected lung (Gavriely et al., 1981).

Computer based analysis of wheeze is now possible with algorithms that relate the amplitude of sharp spectral peaks to the average lung sound amplitude (Baughman and Loudon, 1984, Shabtai-Musih et al., 1992). Beck et al. investigated histamine challenge in 12 children and analysed computerised lung sounds, including wheeze (Beck et al., 1992). Prior to using computer analysis of lung sounds, the histamine challenge, as a

means of evaluation of asthma, was stopped at the point where wheezes were detected by a stethoscope or microphone placed over the trachea.

Other authors have also previously investigated analysis of wheeze as a means of identifying respiratory abnormalities earlier than the awareness and reporting of these abnormalities from patient's themselves (Sanchez et al., 1993). However, in 1993 Sanchez et al. reported findings from their study of 23 CF patients and found that although wheeze is a specific indicator of bronchial hyper-responsiveness, wheeze was absent in 50 % of the CF patients who tested positive with methacholine (Sanchez et al., 1993). In addition, of the subjects who did not respond based on spirometric parameters to the methacholine test, none of them developed wheeze (n = 13), yielding a specificity of 100% (Sanchez et al., 1993). However, it should be noted that the results of the above studies were from studies with small subject numbers.

Crackles

Crackles are another acoustic term that is used in respiratory medicine. Detailed in an early Lancet article by Forgacs in 1967 (Forgacs, 1967), crackles were described as "miniature explosions, heard much more often during inspiration than during expiration. Their pattern is remarkably constant." Crackles are short discontinuous explosive sounds with a duration of less than 20 milliseconds (Pasterkamp et al., 1997). Fine crackles have been defined with a duration of 5 msec and typical frequency of 650 Hz and coarse crackles with a duration of 15 msec and a typical frequency of 350 Hz (Bohadana et al., 2014).

Murphy et al. examined the waveform of fine and coarse crackles in subjects with fibrotic lung disease (Murphy et al., 1977). In the study by Murphy et al., time expanded wave form analysis provided reproducible visual displays that allowed documentation of the differentiating features of lung sounds and enhanced the diagnostic utility of the sounds (Murphy et al., 1977). They found that in these patients, the fine crackles were shorter in duration and thus had higher frequency content than the coarse crackles found in subjects with pneumonia (Murphy et al., 1977). Murphy et al. reported that most crackles have a duration range from 1 to 10 milliseconds and show a great diversity of patterns with large variations in the period of the deflections, that is the length in time of the individual cycles, and in the total number of cycles (Murphy et al., 1977). Crackles have a distinctive appearance in time-expanded waveform analysis: a sudden short deflection followed by deflections with greater amplitude (Charbonneau et al., 2000). It has been proposed that fast Fourier transformation is not as useful in analysing the crackles as they are short bursts of sound. A sampling rate of 5,512 Hz provides a sufficient frequency range for the analysis of crackles (ie. 0 - 2700 Hz). However, the study of several fine crackles may require a wider range of analysis and hence the use of a sampling rate of greater than or equal to 11,025 Hz is recommended (Charbonneau et al., 2000). In more detail, the following measurements can be applied to characterise waveform of crackles: 1. The initial deflection width (IDW) – the duration of the first deflection of the crackles; 2. Two-cycle duration (2CD) – duration of the first 2 cycles of the crackles; and 3. The largest deflection width (LDW) - the width of the largest deflection of the crackles. The most commonly used indices for crackles are: the time duration of the initial deflection and the duration of the first two cycles of the waveform (Fredberg and Holford, 1983, Pasterkamp et al., 1997).

Based on guidelines from the ATS in 1977, the mean durations of IDW and 2CD of fine crackles are 0.7 and 5 milliseconds, and those of coarse crackles are 1.5 to 10 milliseconds (Cugell et al., 1977). The latest published guidelines from CORSA have proposed the 2CD of fine crackles is <10 milliseconds and that of coarse crackles >10 milliseconds (Sovijarvi et al., 2000). The frequency range of the crackles sound is 60 to 2000 Hz, with the major contribution being in the range of 60 to 1200 Hz (Abbas and Fahim, 2010). Hoevers and Loudon proposed a different set of parameters to characterise crackles, namely, largest deflection width (LDW1); which is the duration of the largest deflection of the crackle (Hoevers and Loudon, 1990).

In interstitial lung disease, the number of crackles has been associated with the severity of the pulmonary disease (Epler et al., 1978). By using the timing and waveform characteristics of crackles, a two-dimensional discriminant analysis can be applied as suggested by Sovijari et al. (Sovijärvi et al., 1996).

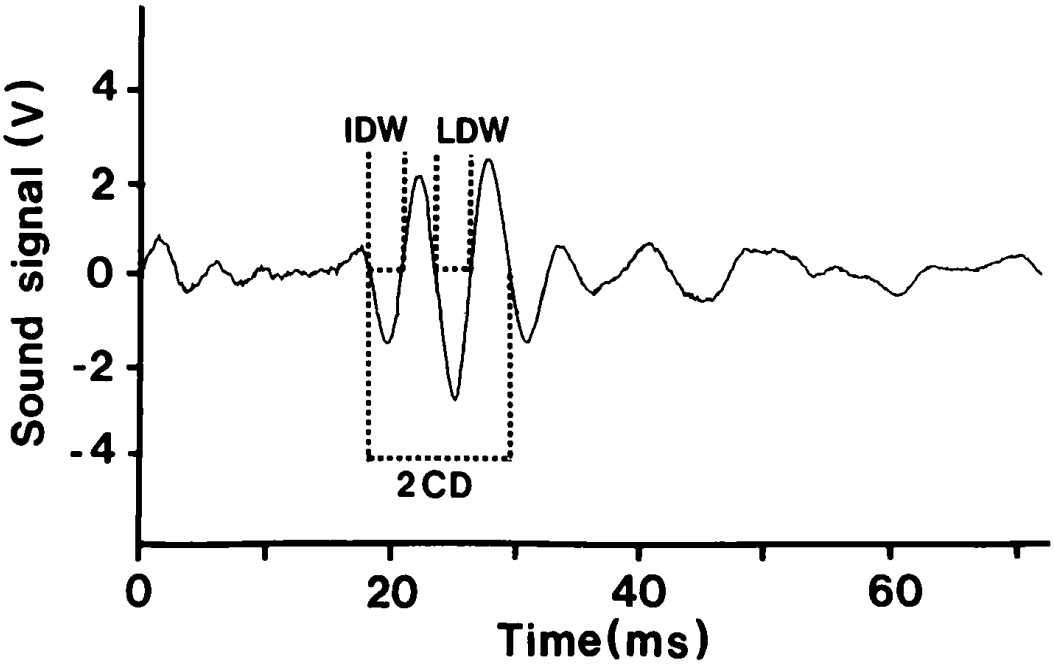

Figure 3.3 Waveform parameters of crackles in time-expanded waveform display. IDW: initial deflection width; 2CD: two-cycle duration; LDW: largest deflection width. Reproduced from Sovijärvi et al. Figure 1 p 172. (Sovijärvi et al., 1996).

Sovijärvi et al. compared the timing and wave form variables of crackles using discriminant analysis. The paired Mahalanobis distances (measure of how many standard deviations away a point is from the mean of the distribution) between the data of different disease groups were used to describe the relative difference between two crackle variables simultaneously. The differences between the disease groups were visualised using a two-dimensional display of individual data and ellipses (Figure 3.4). The middle point of an ellipse represented the mean values of the variables of the groups, and the area of an ellipse is outlined by the standard deviations of the same variables (Figure 3.4).

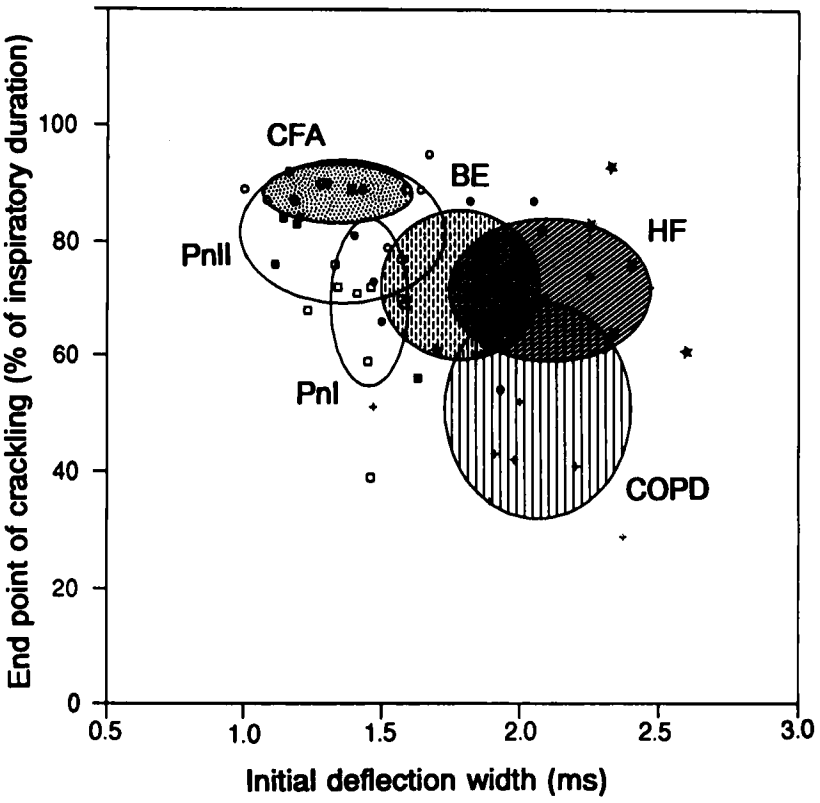

Figure 3.4 Two-dimensional illustration of end-point crackling - as the timing variable and Initial deflection width (IDW) as the waveform variable in: crypogenic fibrosing alveolitis (CFA; n=10), bronchiectasis (BE; n=10), COPD (n=10), heart failure (HF; n=10), acute pneumonia (PnI; n=11) and pneumonia in the recovery stage (PnII; n=9). Sovijärvi et al.: Figure 2, page 175 (Sovijärvi et al., 1996).

The two dimensional distances between the patient groups (cryptogenic fibrosing alveolitis, bronchiectasis, COPD, heart failure, acute pneumonia and recovery from pneumonia) were the largest by combining the IDW and the end-point of crackling (Sovijärvi et al., 1996). This end point of crackling (percentage of duration of inspiration) showed a very high discrimination power between the different disease groups (F-power 12.46, $p < 0.0001$) (Sovijärvi et al., 1996). IDW seemed to be the best waveform variable for separating the diseases (F-value 18.55, $p < 0.0001$) (Sovijärvi et

al., 1996). The discriminating property of 2CD was slightly lower (F-value 15.14, $p < 0.0001$) (Sovijärvi et al., 1996). As discussed by Sovijärvi et al. 1996, in previous studies, the waveform variables IDW, 2CD (Murphy et al., 1977) and LDW (Hoevers and Loudon, 1990) were used to classify crackles into either fine or coarse crackles, however, this kind of classification has been shown to have only a limited value in the separation of pulmonary diseases. Sovijärvi et al. concluded that two dimensional analysis was better able to separate the diseases than was found for single-dimensional analyses of the same crackle data (Piirila et al., 1991, Sovijärvi et al., 1996). Two-dimensional analysis also offers a new opportunity regarding the visual presentation of both the timing and waveform characteristics of crackles. The present study investigating the capabilities of the Sonomat enabled further analysis of these waveforms and timing of adventitial sounds. However, it should be noted that the foam used in the Sonomat mattress may be different from other measurement devices. In addition, the sounds from the subject needed to pass through their clothes and bedding which may dampen the sounds recorded by the Sonomat.

There have been a number of studies investigating devices to identify crackles automatically (Kaisla et al., 1991, Murphy et al., 1989, Pasika and Pengelly, 1994, Pasterkamp et al., 1997, Sarkar et al., 2015, Sovijarvi et al., 2000). However, to date, no one device has been utilised universally.

Sahgal described a method of recording breath sounds and adventitial sounds with remote respiratory monitoring capability that integrates the various techniques used to detect abnormal lung sounds (Sahgal, 2011). A specifically designed software platform

employing LabVIEW software was used to design a system that monitored the respiratory sounds of the patient. The program calculated the respiratory rate, displayed the time expanded waveform of the lung sound, and computed the fast Fourier transform and short-time Fourier transform to present the power spectrum and spectrogram respectively. These parameters were then transmitted synchronously to the remote station using the Internet for online monitoring of the patient (Sahgal, 2011). The power spectrum is the frequency domain data representing the power distribution of a sound with respect to frequency. As discussed in their results, crackle sounds generally occur during inspiration and appear in the time domain at regular intervals with extremely low amplitude (Sahgal, 2011). Their frequency usually ranges from 100 to 2000 Hz or even higher. In the power spectrum of crackle sounds, the main frequency ranged from 0 to 600 Hz (Sahgal, 2011).

Cough

Cough as a respiratory reflex is characterised by sudden expulsion of air at a high velocity accompanied by a transient sound of varying pitch and intensity. One single cough consists of an inspiratory phase followed by an expiratory effort with the glottis closed (compressive phase) and the sudden opening of the glottis with rapid expiratory airflows (expulsive phase) (Sovijarvi et al., 2000).

The sound from a cough is transient with a frequency range between 50 and 3000 Hz. The characteristics of cough sounds are different in different pulmonary diseases (Sovijarvi et al., 2000).

In our CF population with bronchiectasis, we were interested in cough, crackles and wheeze as these adventitial sounds may reflect the presence of sputum retention. As CF respiratory disease progresses, the accumulation of sputum and mucus plugs leads to further inflammation and parenchymal destruction ultimately leading to respiratory failure. By identifying these adventitial sounds, there is scope to document the presence of sputum in the airways. Changes over time could then be measured, with acute changes likely to reflect the onset of an exacerbation. Earlier detection of the changes in crackles could be similar to daily auscultation. However, this could be burdensome in the long term. Having this auscultatory examination occur automatically may identify changes in adventitial sounds and hence allowing early treatment with the aim to prevent further lung destruction and respiratory failure. Therefore, adequate identification of lung sounds is important in the treatment of adults and children with CF.

3.2 AIM

The aim of this project included: identification of respiratory sounds at night (coughs, crackles and wheezes) based on spectrographic and audio analysis using the Sonomat.

3.3 HYPOTHESIS

We can define and identify respiratory sounds (coughs, crackles and wheezes) based on visual, spectrographic and audio analysis using the Sonomat.

3.4 METHODS OF IDENTIFYING RESPIRATORY SOUNDS

3.4.1 Subjects

Subjects were recruited from the adult CF Service at Westmead Hospital, Sydney. All subjects had a diagnosis of CF confirmed on genetic testing and / or elevated sweat chloride levels (> 60 mEq/L). Patients attending the adult CF service at Westmead Hospital (aged >18 years) between 1st January 2013 until 30th November 2016 were approached and offered the opportunity to participate in the project.

The protocols were all approved by the Westmead Hospital Human Research Ethics Committee (HREC2012/12/4.9(3627) AU RED HREC/12/WMEAD/427. Written informed consent was obtained for all subjects.

Examples of respiratory sounds were selected from 4 subjects who had undergone an overnight sleep study in the Sleep Lab at Westmead Hospital using the Sonomat. Demographics of the subjects are shown in Table 3.1.

3.4.2 Sonomat

As described in Chapter 2 – Methods, Section 2.7, the Sonomat device contained four identical sensors containing a polyvinylidine fluoride (PVDF) film that generated a voltage when deformed. Sounds were recorded using these 4 sensors as well as two additional room microphones embedded in a foam mattress. Acoustic signals (breath

sounds) were recorded at a sampling frequency of 4000 Hz and movement signals are recorded at a sampling frequency of 250 Hz. Propriety software, Replay, was developed for the exclusive use of the Sonomat data for analysis of signals.

The scoring criteria used for the Sonomat is detailed in Chapter 2 – Methods, section 2.7. Breath sounds that contained periodic components with fundamental frequency peaks from 20-30 Hz up to approximately 250-300 Hz were scored as snores within Sonomat recordings; these could be confirmed aurally using manual replay and manual scoring.

Respiratory sounds were analysed visually and then clarified using the audio replay of sounds. If there was still uncertainty, the sound was analysed using WaveSurfer, a software program to analyse spectrograms (WaveSurfer 1.8.8p4 -1112300908. Copyright © 2000-2011 Jonas Beskow and Kare Sjolander). Interactive sound analysis software was also used to analyse cough sounds using the Raven Pro version 1.4 computer software (Mills et al., 2018).

In keeping with the current consensus of respiratory sounds nomenclature from The European Respiratory Society Task Force on Respiratory Sounds, all respiratory sounds were classified as per these recommendations (Pasterkamp et al., 2016). Cough sounds were identified aurally and visually from normal lung sounds that contained an initial wide distribution of sound frequencies between 50 and 2000 Hz of short duration and high sound intensity which then rapidly tapers off.

Crackles were identified by using visual identification of rapid bursts of sound that are low pitched, high amplitude with a long duration of more than 1 second across both inspiration and expiration.

Finally, wheezes were identified by visual analysis where there was a predominant frequency of approximately 400 Hz at very high intensity with multiple harmonics and duration of more than 500ms.

3.5 RESULTS

Four subjects were selected as a representative group from those subjects who had undergone an overnight sleep study in the sleep laboratory. Demographic details are shown in Table 3.1.

Table 3.1. Demographic Details of Subjects Selected for Respiratory Sound Samples

Respiratory Sound Identified	Subject ID	Age (years)	BMI (kg/m^2)	Genotype	FEV_1 (% pred)	Colonisation
Normal	33	21	19.2	F508del/ G551D	89	MucPSA
Cough	3	28	19.6	F508del/ F508del	51	MucPSA Staph aureus
Crackles	5	31	21.0	F508del/ G542X	59	MucPSA
Wheeze	9	47	27.7	UNK/ UNK	46	MucPSA

N = 4. BMI: body mass index; FEV_1: forced expiratory volume in 1 second; MucPSA: *Pseudomonas aeruginosa*.

Based on the recordings from the Sonomat, different respiratory sounds can be detected and classified as described below.

Normal Lung Sounds

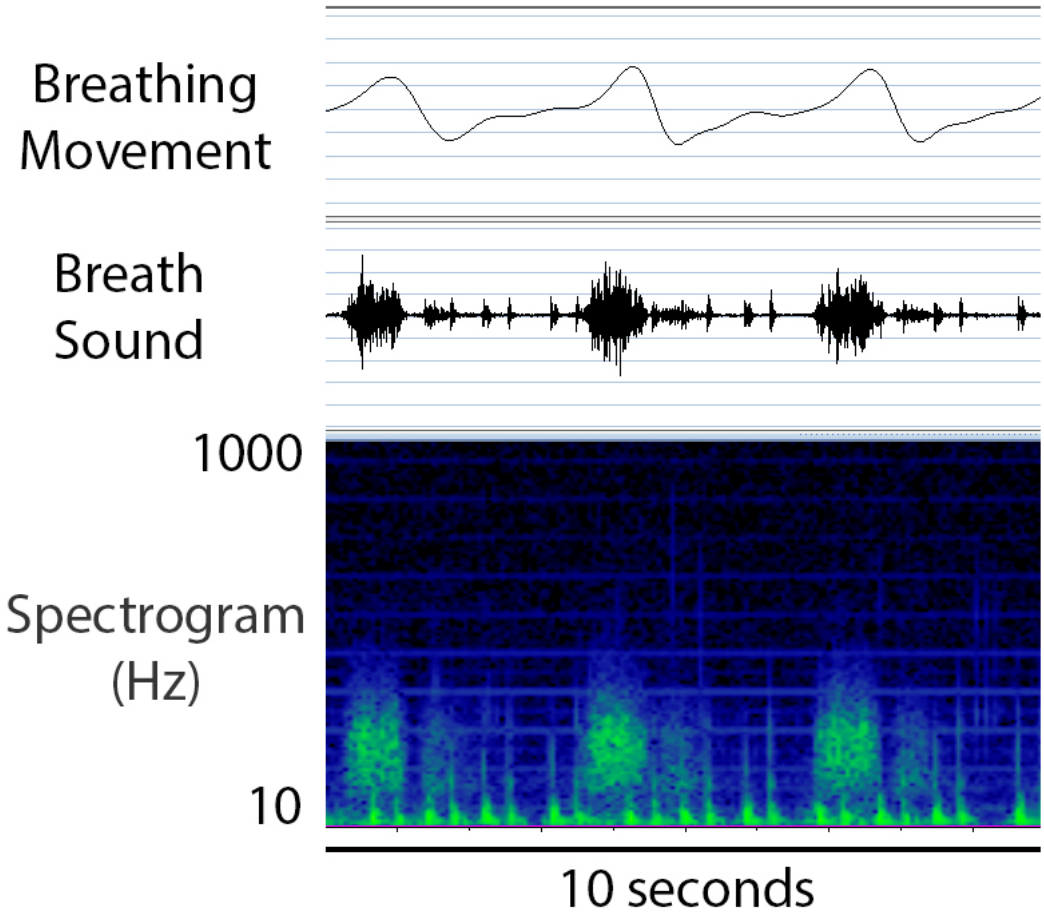

Figure 3.5 Normal Lung Sounds - over 3 breaths in 10 seconds.

The above figure demonstrated 3 consecutive normal lung sounds over a 10 second period in an adult with CF with normal lung function. There was a biphasic signal for inspiration (upward deflection) and expiration (downward deflection) on the breathing movement signal. On the breath sound channel, the amplitude of the sound was shown. Spectral analysis (spectrogram) depicted the different sound frequencies (vertical axis) and intensities (colour of sounds: louder is red and yellow, softer blue and green) versus time. In normal lung sounds, there were no predominant frequencies as shown for the 3 breaths in Figure 3.5. All continuous frequencies (horizontal lines) visible in the background were generated from equipment in the laboratory.

Cough Sounds

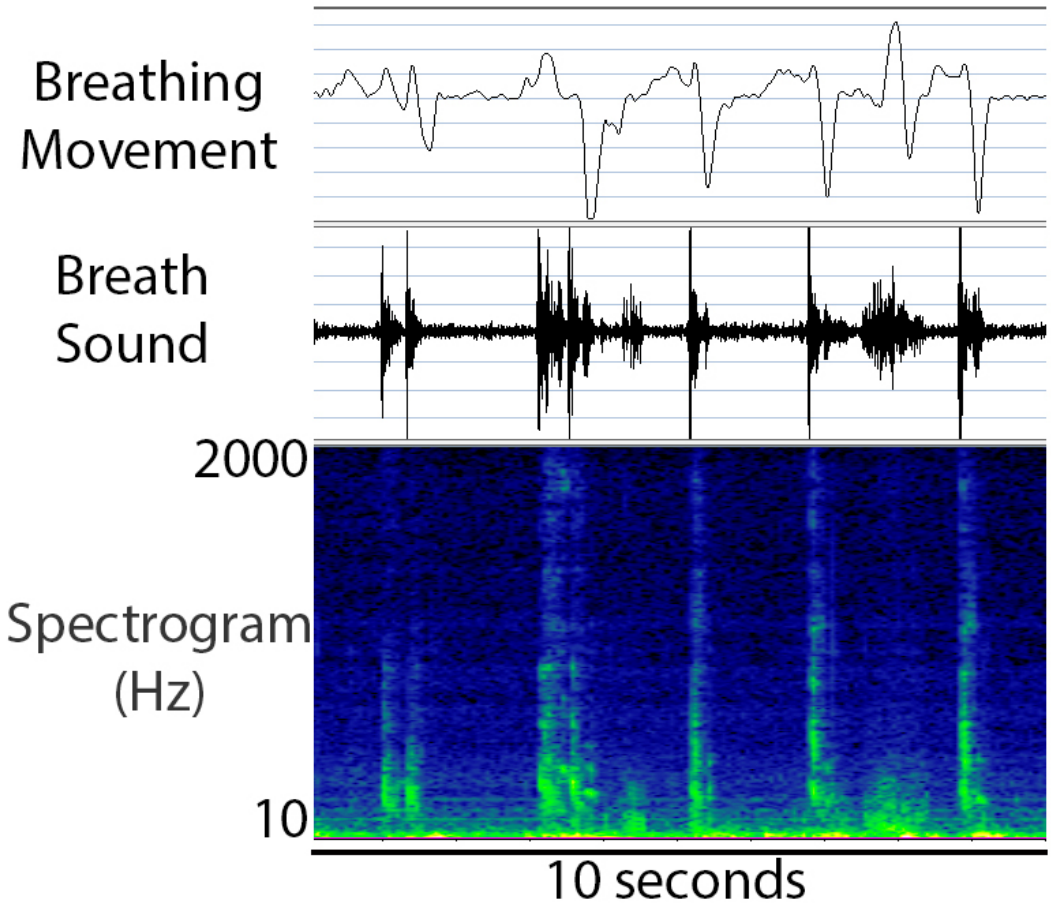

Figure 3.6 Cough Sounds - over 10 seconds

Coughs were identified on the Sonomat data tracings in both the breathing movement and breath sound signals and confirmed using manual audio playback. This figure demonstrated multiple coughs with both single coughs and cough paroxysms (more than 1 cough). There were two short coughs at the beginning of the period followed by a cough paroxysm. Using spectral analysis, these coughs showed a wide distribution of sound frequencies and short duration.

Crackles

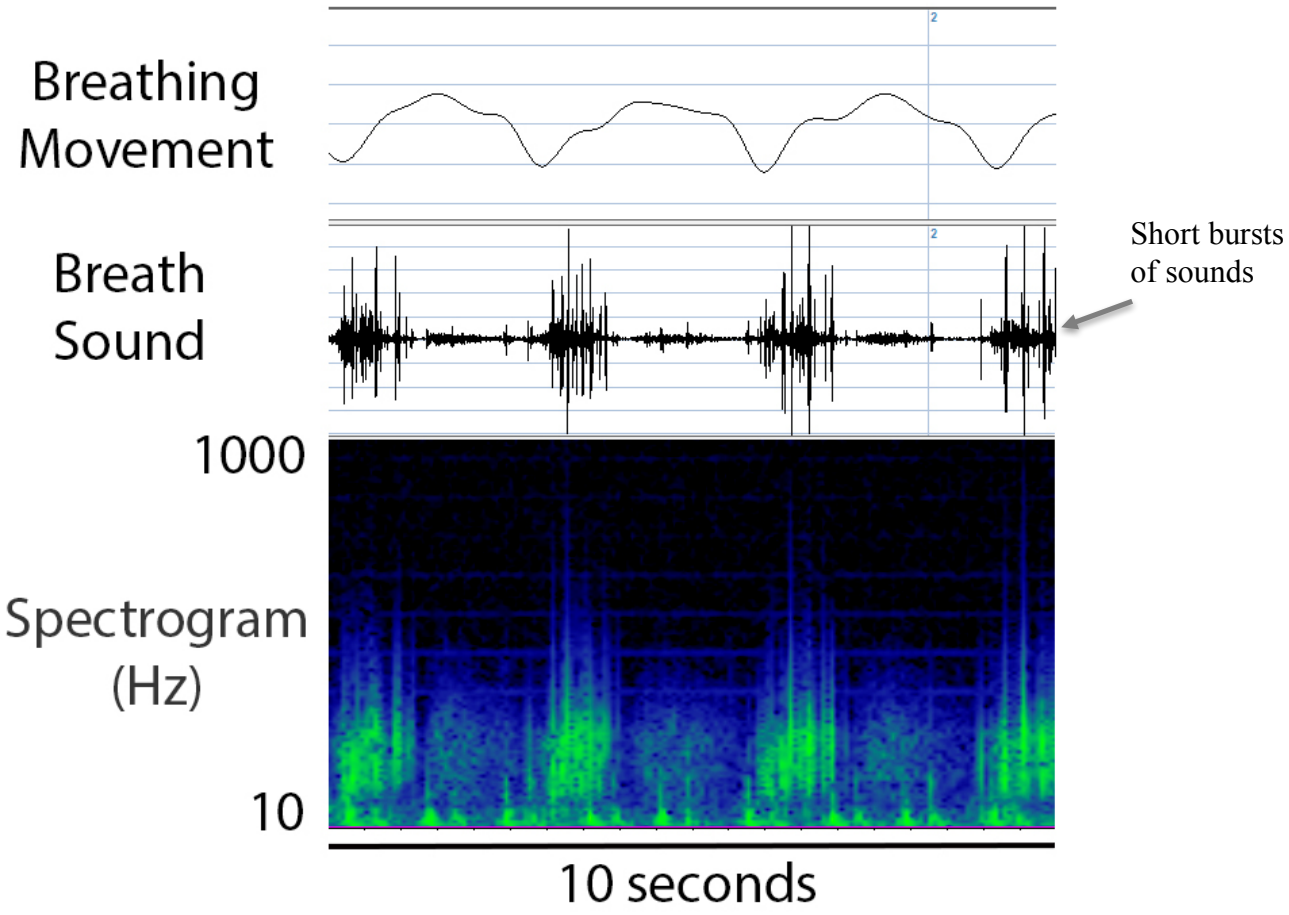

Figure 3.7 Crackles - over 10 seconds

Figure 3.7 showed 4 episodes of expiratory crackles over a 10 second period. The Sonomat was able to differentiate crackles from normal breath sounds due to the presence of short bursts of sound within each breath sound. Crackles were better able to be visualised on breath sound tracings rather than the spectrogram shown above.

Wheezes

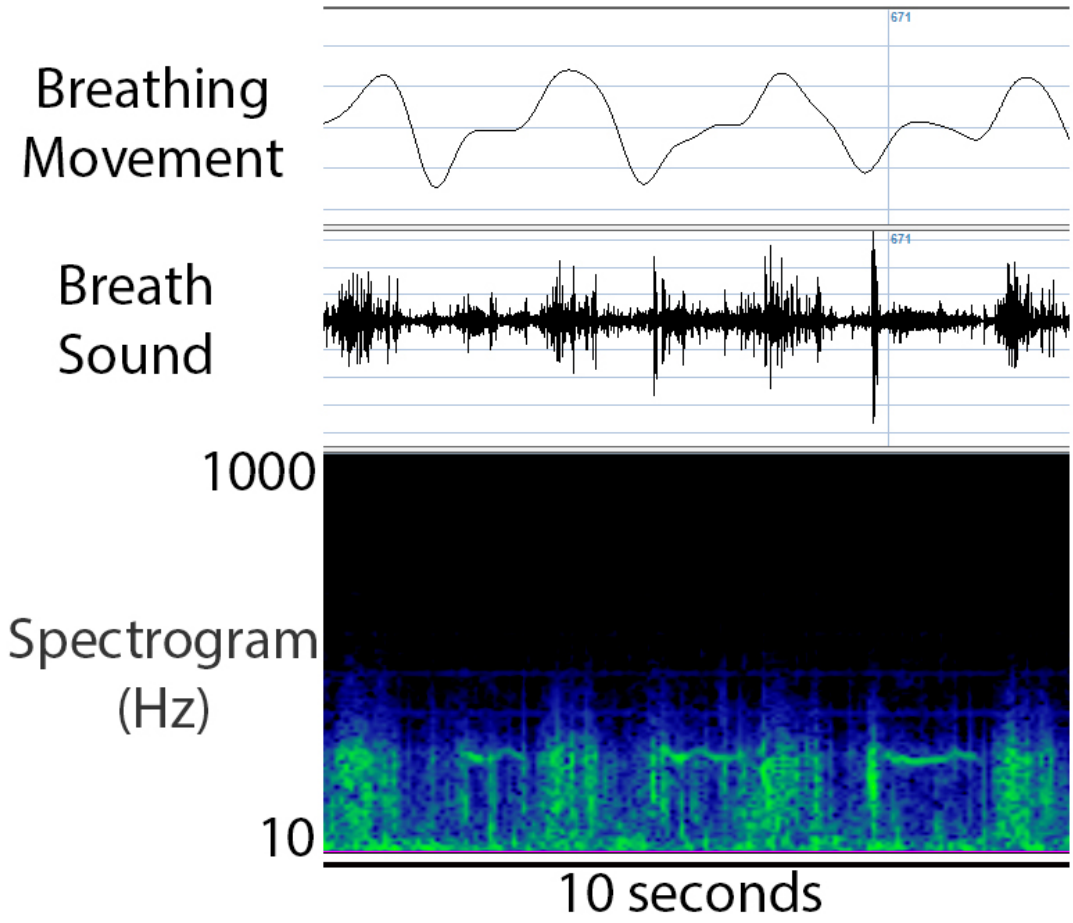

Figure 3.8 Wheezes - over 10 seconds

Using spectral analysis, the figure above showed 3 wheezes with a louder continuous sound at 400Hz.

Snores

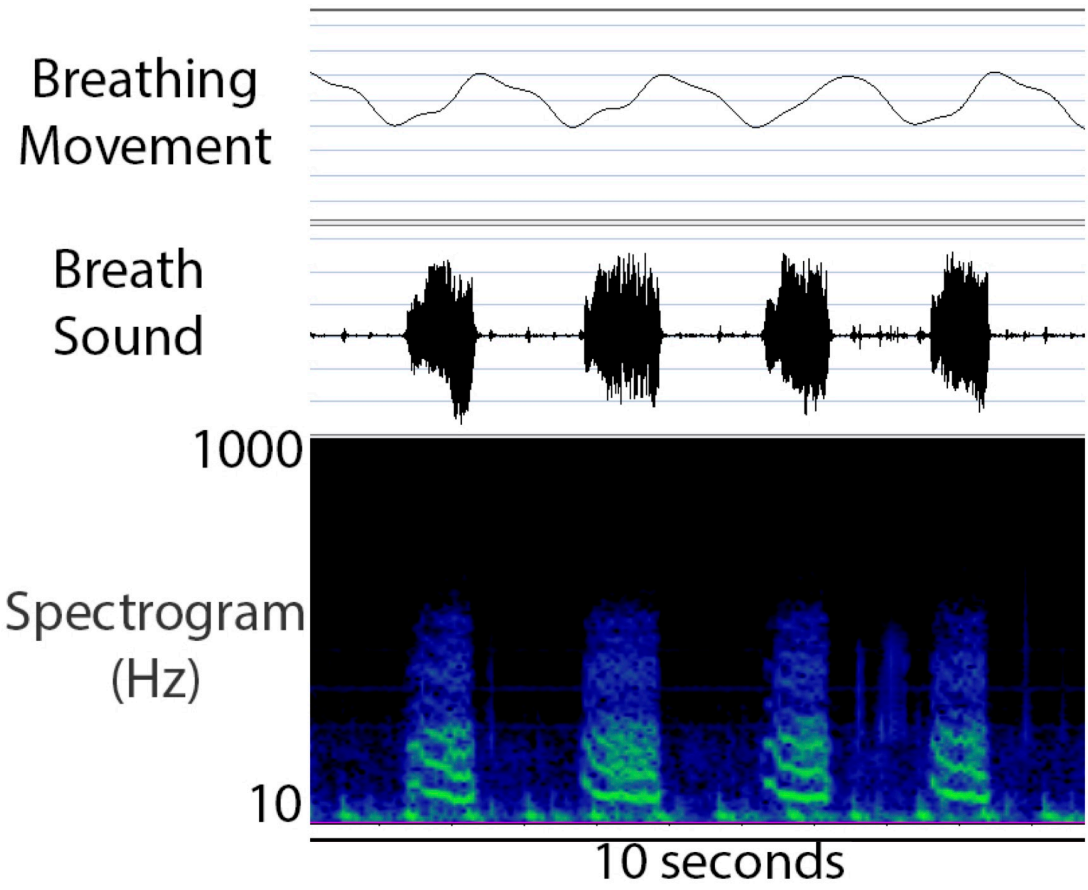

Figure 3.9 Snores - over 10 seconds

The above figure demonstrated 4 expiratory snores over 10 seconds. Distinct bands of colour (green) indicated the frequencies at which the upper airway is vibrating. The lowest band was the fundamental frequency with the higher frequency bands with multiple harmonics.

3.6 DISCUSSION

This study aimed to use the Sonomat to characterise respiratory sounds. The principal characteristics of lung sounds include characterisation of frequency, intensity, duration and quality (Hadjileontiadis, 2008). The time and frequency domain characteristics of the sound signal likely reflect pathological changes that occur with pulmonary disease associated with CF. Using a signal analysis technique (spectrography), abnormal lung sounds can be visually detected as well as audibly confirmed. Our study was similar to a study performed by Saghal et al., who used lung sounds from Stethographics Inc 2007 © (Stethographics) to demonstrate the ability to remotely monitor the respiratory activity of a patient (Sahgal, 2011). Our results are in keeping with those studies documented above including the published papers from Saghal et al. and Bohadana et al. (Bohadana et al., 2014, Sahgal, 2011).

Our study showed the qualitative differences between respiratory sounds. The data analysed above are novel and can be used as a foundation to develop automated algorithms which would classify different respiratory sounds based on their unique frequency, intensity and duration characteristics. Future studies will be useful to analyse respiratory sounds in groups of subjects to categorise parameters which are similar and can be validated between subjects for different respiratory sounds. This particular area of interest has not been demonstrated previously in CF patients and hence, is highly novel. Whilst it was not possible in this thesis to demonstrate the differences of sounds that occur both within subjects and between subjects, further analysis grouping subjects' respiratory sounds will be required to provide adequate

information for the development of algorithms. These grouped data have been collected and are the origin of current novel research investigating sound characteristics in respiratory disease, particularly in relation to cystic fibrosis.

Changes of the presence or absence of respiratory sounds can be useful in the clinical assessment of subjects. For example, increasing presence of crackles may indicate that airway clearance is either suboptimal or not effective. Early identification of such changes in respiratory sounds may allow clinicians to intervene earlier and recommend increasing physiotherapy airway clearance techniques or even prescribe antibiotics (Doring et al., 2012). In addition, automated review of respiratory sounds could provide physicians another method of monitoring patients either in real-time or via telemedicine.

3.7 CONCLUSION

Using the Sonomat, respiratory sounds (normal lung sounds, coughs, crackles and wheezes) were characterised based on spectrographic and audio analysis. In the case of crackles, short bursts of higher amplitude and frequency sound can be identified within each breath. In contrast, wheezes have a loud musical sound at approximately 400 Hz. The Sonomat can be used at a single time point or longitudinally over a number of days or weeks to identify these respiratory sounds in subjects with cystic fibrosis.

CHAPTER 4: CROSS-SECTIONAL OBJECTIVE SLEEP MEASUREMENTS IN ADULTS WITH CYSTIC FIBROSIS

4.1 INTRODUCTION

CF impacts on sleep in a number of ways including sleep fragmentation, sleep disordered breathing, hypoventilation, rhinosinusitis or by coughing due to impaired mucus clearance from the lower airways (Dobbin et al., 2005, Milross et al., 2004, Perin et al., 2012, Spier et al., 1984, Stokes et al., 1980). More than 30 years ago, nocturnal hypoxaemia was identified in adults with severe lung disease due to CF (Francis et al., 1980, Muller et al., 1980, Spier et al., 1984, Tepper et al., 1983). In particular, these authors demonstrated oxygen desaturation during sleep with more severe desaturation during hypoventilation in REM sleep (Francis et al., 1980, Muller et al., 1980, Spier et al., 1984, Tepper et al., 1983). Repeated desaturation during sleep may contribute to the development and progression of cor pulmonale in patients with CF with sustained elevation of pulmonary arterial pressure. Ultimately, the development of cor pulmonale is a poor prognostic factor for survival (Stern et al., 1980).

Whilst polysomnography is the gold standard to investigate sleep disordered breathing, as noted above, it may miss arousals due to cough or other lower airways dysfunction. (See details of polysomnography in Chapter 2 – Methods, Section 2.6).

Non-invasive methods of detecting sleep disordered breathing are providing additional ways to supplement the conventional methods using overnight polysomnography. In 1981, a novel non-invasive method of detecting heart rate and respiration was

investigated by Alihanka et al. (Alihanka et al., 1981). Using a static charge-sensitive bed (SCSB), respiratory movements and the ballistocardiogram (reflecting the strength of the myocardial contraction) were recorded based on body movements inducing a static charge distribution in the "active" layers of the mattress, these "active" layers were two separate plastic layers. These charges induced potential differences between two large metal plates located under the mattress and isolated from each other by a stiff insulating plate. The potential difference between the metal plates was recorded by a conventional differential (AC or DC) amplifier (Alihanka et al., 1981). As more interest has developed into the respiratory regulation during sleep, many disorders including sleep apnoea, sleep disordered breathing and their cardiopulmonary consequences are now being studied. Kirjavainen et al. investigated a sensor mattress used in the detection of sleep apnoea (Kirjavainen et al., 1996). These authors found that in heavy snorers, episodes of high frequency spiking occurred on the static charge sensitive bed (SCSB). Further to night time use, the authors used the bed during a respiratory challenge and found the same results with spike amplitude correlating with breathing frequency and variation in oesophageal pressure (Kirjavainen et al., 1996). To detect abnormalities in breathing at night, Tenhunen et al., 2013, showed that the electromechanical film transducer (Emfit) signal in their SCSB was able to evaluate nocturnal breathing including obstructive and central breathing without the use of oximetry (Tenhunen et al., 2013). Furthermore, the Emfit can be used in all patients and there are no contraindications (Tenhunen et al., 2013).

In a previous study by Dancey et al., PSGs in CF subjects with severe lung disease demonstrated reduced sleep efficiency (71 ± 25 % versus 93 ± 4 %, $p = 0.004$) and higher frequency of awakenings (4.2 ± 2.7/h versus 2.4 ± 1.4/h, $p = 0.06$) compared

with normal subjects (Dancey et al., 2002). As expected, mean nocturnal arterial SaO_2 was lower in CF subjects with severe lung disease (84.4 ± 6.8 % versus 94.3 ± 1.5 %, $p < 0.0001$) which correlated with reduced sleep efficiency (regression coefficient = 0.57, $p = 0.014$) (Dancey et al., 2002).

Perin et al. demonstrated that SpO_2 and end tidal CO_2 during sleep were significantly correlated ($p < 0.001$) with pulmonary function ($r = 0.62$ for FEV_1 and $r = 0.66$ for FVC), awake SpO_2 ($r = 0.90$), at the end of a 6MWT ($r = 0.78$), and end tidal carbon dioxide ($EtCO_2$) values ($r = -0.86$) (Perin et al., 2012). Furthermore, awake SpO_2 at rest was the single best variable associated with sleep desaturation (relative risk: 0.48, 95 % CI = 0.33 - 0.70, $p < 0.001$) (Perin et al., 2012). All CF patients with resting $SpO_2 <$ 94 % demonstrated significant nocturnal desaturation (Perin et al., 2012). These previous studies were examining people with CF who had established daytime respiratory failure rather than looking at the spectrum of lung disease in people with CF who have differing levels of lung function including those people with normal lung function.

The correlation of disease severity in patients with CF and increased risk of sleep apnoea was investigated by Veronezi et al. (Veronezi et al., 2015). This study of 34 young CF patients (mean age 15.9 years) with a mean post-bronchodilator FEV_1 of 71% predicted did not find a correlation between FEV_1 and AHI, similar to those findings of Ramos et al. (Veronezi et al., 2015, Ramos et al., 2011). There are few studies investigating subjects with only mild to moderate lung function. Hence, the subjects in the current novel study had a wide range of severity of lung function including normal lung function.

The Sonomat, the non-invasive device used in this current study, has been validated for the diagnosis of sleep apnoea similar to the gold standard PSG (Norman et al., 2014). As part of these validation studies, subjects from the Westmead Sleep Investigation and Research Centre participated in paired studies involving overnight PSG and Sonomat studies, similar to those performed in the current study. The data from the validation research indicated that the Sonomat was reliable and accurate for the diagnosis of OSA (Norman et al., 2014). Using Bland-Altman analysis of the AHI, there was positive agreement between the devices, particularly at levels around common diagnostic thresholds (Norman et al., 2014). Further studies are under way to examine the accuracy of the Sonomat in a variety of patient groups, including in asthma patients and our own patient group studied for this thesis.

Details of the Sonomat have been documented in Chapter 2 – Methods. As described, using sensors to detect sounds and body movements, the Sonomat was able to record and analyse respiratory events such as apnoea, hypopnoeas and important respiratory sounds including, coughs, crackles and snores. Hence, the Sonomat can detect abnormal breathing during sleep to allow the determination of breathing disordered sleep (due to coughs or crackles) as well as the presence of sleep disordered breathing (apnoeas or hypopnoeas).

To detect breathing abnormalities and lower airway dysfunction during sleep, a more sensitive testing system than the PSG is required. Furthermore, PSG is an in-laboratory test, which is not appropriate for long term repeated use. A home-based non-invasive simple recording device, such as the Sonomat, is an ideal system which can be used

long term. This device also has the advantage of being able to detect abnormalities of sleep disordered breathing.

As people with CF are now living longer due to advances in medical care, the median survival is now greater than 40 years in Australia (Ruseckaite et al., 2018). This demographic shift has resulted in the need for adult-specific CF care programs to examine sleep disturbance caused by cough or breathing disorders during sleep. Thus, this study examined the spectrum of sleep abnormalities in adults with CF (including those with normal lung function) with the use of PSG and the addition of the novel measurement device, the Sonomat.

4.2 AIM

The aim of this study was to compare and contrast abnormalities in sleep and breathing using the PSG and Sonomat across a range of lung function in adults with CF.

4.3 HYPOTHESES

1. Abnormalities in sleep and breathing occur in adults with CF subjects with a wide range of lung disease.
2. The Sonomat can describe abnormalities in sleep and breathing using additional respiratory parameters not detected by PSG.

4.4 METHODS

4.4.1 Subjects

Adults with CF were recruited from the Adult CF Service Westmead to undergo sleep testing (using the Sonomat simultaneously with the PSG) at the Westmead Sleep Investigation and Research Centre. CF diagnosis had been confirmed previously based on standard clinical criteria as noted in Chapter 2. The study was performed at the end of a hospital admission for treatment of a pulmonary exacerbation with the intention that the subjects achieved the best level of lung function possible. The protocols were approved by the Westmead Hospital Human Research Ethics Committee (HREC2012/12/4.9(3627) AU RED HREC/12/WMEAD/427). Written informed consent was obtained for all participants.

All CF participants underwent a comprehensive clinical evaluation. Basic demographic information was recorded at the time of enrolment. Standard anthropometric measurements were obtained including: weight, height, body mass index (BMI).

4.4.2 Lung Function

Spirometry was performed according to ATS/ERS criteria (Miller et al., 2005) as described in Chapter 2 - Methods. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were recorded or tested. Predicted spirometric parameters were derived using reference values from Hankinson et al. (Hankinson et al., 1999).

4.4.3 Polysomnography

As described in Chapter 2 – Methods, Section 2.6, standard overnight in-laboratory polysomnographic recordings were performed using a computerised acquisition system (Compumedics). The PSG recorded the following signals: electro-encephalogram (EEG), electro-oculogram (EOG), submental electro-myogram (EMG), electro-cardiogram (ECG), thoraco-abdominal excursion (respiratory induction plethysmography), nasal flow (pressure transducer), oro-nasal flow (thermistor), snoring sounds (using a calibrated room sound meter, pulse oximetry (SpO_2), leg movements, and body position.

Polysomnography Scoring

All PSG studies were scored according to the American Academy of Sleep Medicine (AASM) guidelines for scoring sleep stages, arousals, and respiratory events with the alternate (Type B) hypopnoea criteria used (Iber et al., 2007). The studies were all scored using the 2007 AASM guidelines prior to the sleep service adopting the revised AASM guidelines published in 2012 (Berry et al., 2012). Full details of scoring are discussed in Chapter 2 – Methods, Section 2.6. Sleep efficiency, Arousal index (AI), Apnoea-Hypopnoea index (AHI), and Respiratory disturbance index (RDI), were all calculated.

4.4.4 Sonomat

The Sonomat device was used for this study as described in Chapter 2 - Methods. Four identical sensors were embedded into the foam mattress and these contained a

polyvinylidine fluoride foam that generated a voltage when deformed. Sounds were recorded using these 4 sensors as well two additional room microphones embedded in the foam mattress. The mattress was placed directly on top of the bed in the PSG laboratory covered with a sheet and the subject laid on the Sonomat but was not attached to the Sonomat without any physical attachments to the mat.

Acoustic signals were recorded at a sampling frequency of 4000 Hz and movement signals are recorded at a sampling frequency of 250 Hz. The software, Replay, was used to analyse the data from the Sonomat.

Sonomat Scoring Criteria

The analysis of the study began after the last of a series of frequent body movements that followed the subject lying down with the intention to sleep. Analysis stopped when frequent body movements persisted or sounds indicated that the subject was awake. The duration of significant body movements indicating wakefulness during the night was removed from the total recording time (TRT) to calculate the "quiescent duration" (Qd or sleep time). This Qd or sleep time duration, contained all periods of postural immobility, was used as the estimate of total sleep time (TST). Sonomat respiratory events were visually scored and were also replayed through audio speakers for further clarification of events. The apnoea-hypopnoea index (AHI) from the Sonomat studies (AHI MAT) was generated by dividing the number of valid respiratory events by the Qd.

Breath sounds were scored throughout the night as detailed in Chapter 2 – Methods. These breath sounds included: normal breath sounds, snores, coughs, crackles and wheezes. At any time point during the study, respiratory sounds, such as cough or snores may co-exist with the presence of crackles and apnoeas / hypopnoeas. Duration of each of the above breath sounds per hour was calculated by dividing the total duration of each breath sound by the Qd (in hours). For cough, the total number of coughs was also summed together in three categories: 1. Single cough; 2. Two to five coughs; and 3. Greater than 5 coughs. In addition, duration of cough during sleep and cough during awake time within the sleep period were calculated. The Sonomat produces a calculation for AHI based on apnoeas or hypopnoeas with cessation or reduction of body and chest movements on movement channels. As there are no oximetry data for the Sonomat, the Sonomat "AHI" most closely resembles RDI on the PSG. The RDI on the PSG is calculated based on the inclusion of apnoeas, hypopnoeas and respiratory effort related arousals (RERAs).

4.4.5 Statistical Analyses

Statistical and graphical analyses were performed using SPPS v.22 (SPSS Inc., IL, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). Normally distributed data are presented as mean ± standard deviation (SD), and non-normally distributed data are presented as median and interquartile range (IQR).

4.5 RESULTS

The paired sleep studies were performed in 40 subjects (16 male, aged 33.8 ± 10.8 years), with demographic data reported in Table 4.1.

Table 4.1 Baseline Characteristics

Characteristic	
Male (n, %)	16, 40
Age, years (mean ± SD) (range)	33.8 ± 10.8 (20 to 67)
BMI, kg/m^2 (mean ± SD)	21.6 ± 3.2
Genotype, F508del Homozygous (n, %)	23, 58
FEV_1, % predicted (mean ± SD) (range)	47.9 ± 17.8 (21.0 to 100.0)
MucPSA (n, %)	27, 68
Pancreatic Sufficient (n, %)	3, 8
Diabetes (n, %)	7, 18

N = 40 subjects. Data expressed as mean ± SD. BMI: body mass index; FEV_1: forced expiratory volume in 1 second. MucPSA: mucoid *Pseudomonas aeruginosa*.

This group of subjects had moderately severe lung disease with mean FEV_1 % predicted of 47.9 % (range between 21 to 100 FEV_1 % predicted). All subjects were using preventer bronchodilator therapy (inhaled corticosteroids combined with long acting beta agonist). Nebulised dornase-alpha was used in 85 % of subjects, of these subjects, 21 also used hypertonic saline as a mucolytic medication. Six subjects did not use regular oral aminoglycosides and thirteen subjects were on oral corticosteroid therapy (dose ranging from 5 to 15 mg per day).

Table 4.2 PSG Sleep Characteristics

PSG Sleep Characteristic	
Sleep Efficiency, %	78.7 ± 13.7
Arousal Index, events per hour	17.9 ± 8.3
RDI, events per hour	5.6 (8.3)
AHI, events per hour	1.1 (2.6)
Total sleep time, minutes	341.6 ± 66.6
REM sleep, %	15.9 ± 6.9
NREM sleep, %	83.1 ± 6.9
WASO, minutes	53.0 (93.5)
Baseline SpO_2, %	95.0 (1.8)
REM min saturation, %	88.5 (6.5)
NREM min saturation %	89.0 (4.3)
Mean SpO_2 desaturation during sleep, %	3.0 (4.0)
Mean SpO_2 during sleep, %	92.4 ± 3.0
ODI, events per hour	0.3 (1.7)
Nadir SpO_2, %	87.6 ± 4.6
Pulse rate, bpm	85.5 ± 13.7

N = 40 subjects. Data expressed as mean ± SD (for normally distributed data) or median (IQR) (for non-normally distributed data). PSG: Polysomnogram; RDI: Respiratory Disturbance Index; AHI: Apnoea Hypopnoea Index; REM: rapid eye movement sleep; NREM: non-rapid eye movement sleep; WASO: wake after sleep onset; SpO_2: oxygen saturation; min: minimum; ODI: oxygen desaturation index; bpm: beats per minute

Table 4.3 PSG Sleep Arousal Results

Arousals	**Median (IQR)**
Respiratory Arousals / hr	4.5 (8.5)
Leg Arousals / hr	0.0 (0.2)
Spontaneous Arousals / hr	8.2 (9.1)

In this group of adults with CF with moderately severe lung disease, most parameters measured by PSG were close to the normal reference ranges (AASM, 2014, Bonnet and Arand, 2007). Overall, the RDI was mildly increased with a median of 5.6 events per hour (normal < 5 events per hour) (AASM, 2014). The AHI was within the normal reference range at less than 5 events per hour (median 1.1 events per hour). There was one outlier, subject 9, who had previously been diagnosed with severe obstructive sleep apnoea (AHI 53 events per hour of sleep) and uses CPAP therapy nightly. See Figures 4.1 and 4.2 below.

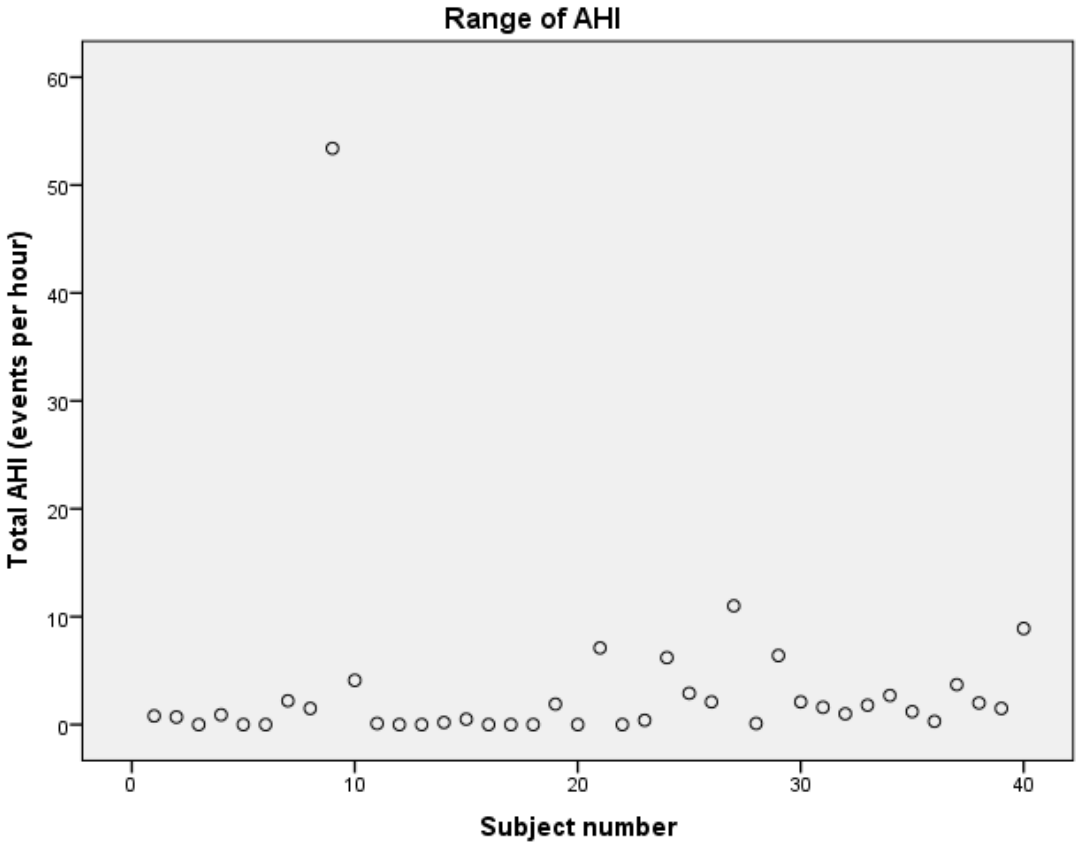

Figure 4.1 Range of Apnoea-Hypopnoea Index (AHI)

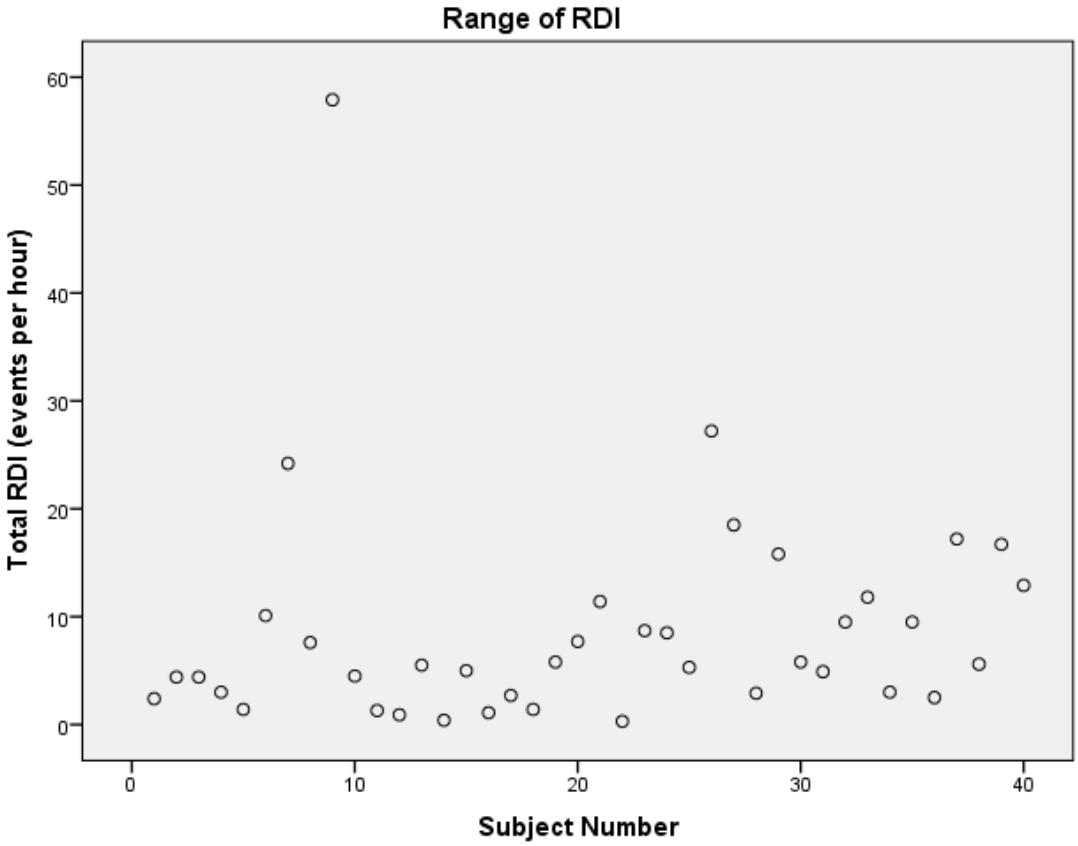

Figure 4.2 Range of Respiratory Disturbance Index (RDI)

Mean SpO_2 during sleep was mildly reduced with mean of 92.4 % (SD ± 3.0) and nadir SpO_2 was also mildly reduced with mean of 87.6 % (SD ± 4.6). As shown above, arousals were all within reference ranges even when considering altered reference values in the younger age groups, where mean arousal index for 31 to 40 years has been reported as 16.8 ± 6.2 events per hour (Bonnet and Arand, 2007). The arousal index was found to be weakly negatively correlated with nadir SpO_2 ($p = 0.006$; $r^2 = 0.190$) but was not found to be correlated with other oximetry parameters including: baseline SpO_2 and mean SpO_2 during sleep time ($p = 0.556$ and 0.132; $r^2 = 0.002$ and 0.049; respectively).

Sonomat

Table 4.4 Sonomat Sleep Characteristics

Sonomat Sleep Characteristic	
Sleep Efficiency, % (based on Qd)	93.7 ± 4.2
Total sleep time, minutes	397.5 ± 55.2
WASO, minutes	26.5 ± 17.9
Total AHI, events per hour	3.4 (10.0)
Crackles, % of sleep time	19.9 (52.0)
Cough, % of sleep time	0.2 (0.5)
Nocturnal awake time with cough, seconds	8.9 (18.2)
Total sleep time with cough, seconds	53.5 (131.0)
Cough, total number of episodes of: 1 cough 2 - 5 coughs > 5 coughs	 1.0 (5.8) 12.0 (38.8) 1.0 (4.0)
Snores, % of sleep time	5.1 (16.8)

N = 40 subjects. Data expressed as: mean ± SD or median (IQR). Qd: quiescent duration; WASO: Wake after sleep onset; AHI: apnoea-hypopnoea index.

The sleep efficiency based on the Sonomat was adequate in this group of CF subjects with a mean sleep efficiency of 93.7 %. The % of total sleep time (Quiescent duration - Qd) with crackles was 19.9 % (IQR 52.0). Cough was minimally recorded at only 0.2 % (IQR 0.5) during sleep. The % of sleep time spent snoring was 5.1 % (IQR 16.8). It should be noted coughs were visualised both whilst the subject was awake as well as

during quiescent time to look at consistency of coughs within subjects. However, data presented below showed specific examination of cough during quiescence (sleep) as well as awake time during the total recording time (TRT).

Specific examination of cough in these subjects required analysis of cough sounds during awake time at night, not just coughs occurring during sleep to look at consistency of coughs within subjects. Assessment of cough during sleep and awake time during night demonstrated a cumulative median cough time during sleep of 53.5 seconds. Cough during total recording time demonstrated a median of 8.9 seconds (range 0 to 734 seconds through the night). Dividing the number of cough episodes into three categories, demonstrated a wide variation between subjects with some subjects only ever performing single coughs, others performing cough paroxysms (greater or equal to 2 coughs) interspersed with single coughs during the night of study. As shown in Table 4.4, cough episodes of between 2 and 5 coughs per episode were more commonly demonstrated than either single coughs or cough paroxysms of more than 5 coughs per coughing episode.

An example of a hypnogram of a subject with coughs occurring both during sleep as well as during awake time is shown below in Figure 4.3. For this subject, prior to analysis start time, coughs occurred up until quiescent time (indicating sleep). Throughout the total recording time there were burst of coughs but not as numerous as the number occurring during awake time.

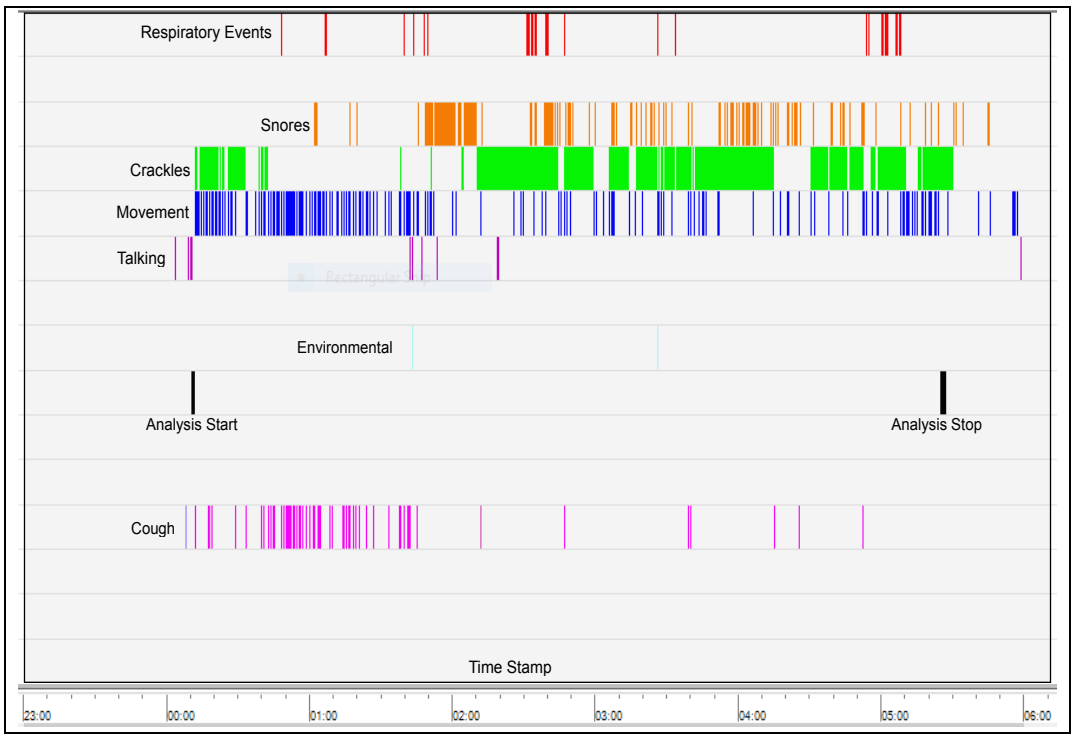

Figure 4.3 Hypnogram of One Subject with Coughs.

Multiple events were seen in the above hypnogram including: occasional respiratory events (red, top row), snores (orange), crackles (bright green), movements (blue), talking (purple), environmental – such as external door close (bright blue), coughs (pink, bottom row). Analysis started (1st black line) after the last of a series of frequent body movements that followed the subject lying down with the intention to sleep. Analysis stopped (2nd dark black line) when frequent body movements persisted or sounds indicated that the subject was awake. Qd is the duration of time where no body movements were detected during the recording time.

Comparison of Sonomat and PSG Data

The sleep characteristics from the Sonomat and PSG are shown in Table 4.5 below.

Table 4.5 Sonomat and PSG Data

Sleep Characteristic	Sonomat	PSG	Correlation Sonomat and PSG	
			p-value	r^2
Sleep efficiency, %	94.7 (3.6)	79.0 (16.5)	0.001	0.443
AHI, events per hour	3.4 (10.0)	1.1 (2.3)	0.001	0.788
Respiratory events (apnoeas/hypopnoeas), events per hour	3.4 (10.0) (Sonomat AHI)	5.5 (7.6) (PSG RDI)	0.001	0.561

N = 40 subjects. Data expressed as Median (IQR). PSG: Polysomnogram; AHI: Apnoea-hypopnoea index; RDI: Respiratory disturbance index. Correlation is significant at the 0.05 level (2-tailed).

Although the Sonomat showed a high sleep efficiency overall, there was a statistically significant positive correlation between sleep efficiency in the Sonomat and the PSG (r^2 = 0.443, p = 0.001), Figure 4.4. Overall, the Sonomat tended to overestimate the sleep efficiency as well as the PSG AHI but underestimate the PSG RDI. The Sonomat overestimated the period of quiescence as the Qd was based on absence of body movements as a surrogate for sleep duration. The AHI was positively correlated

between Sonomat and PSG (r^2 = 0.788, p = 0.001), as shown in Figure 4.5. In addition, there was a moderately strong correlation between Sonomat AHI and PSG RDI (r^2 = 0.561, p = 0.001), as demonstrated in Figure 4.6 below.

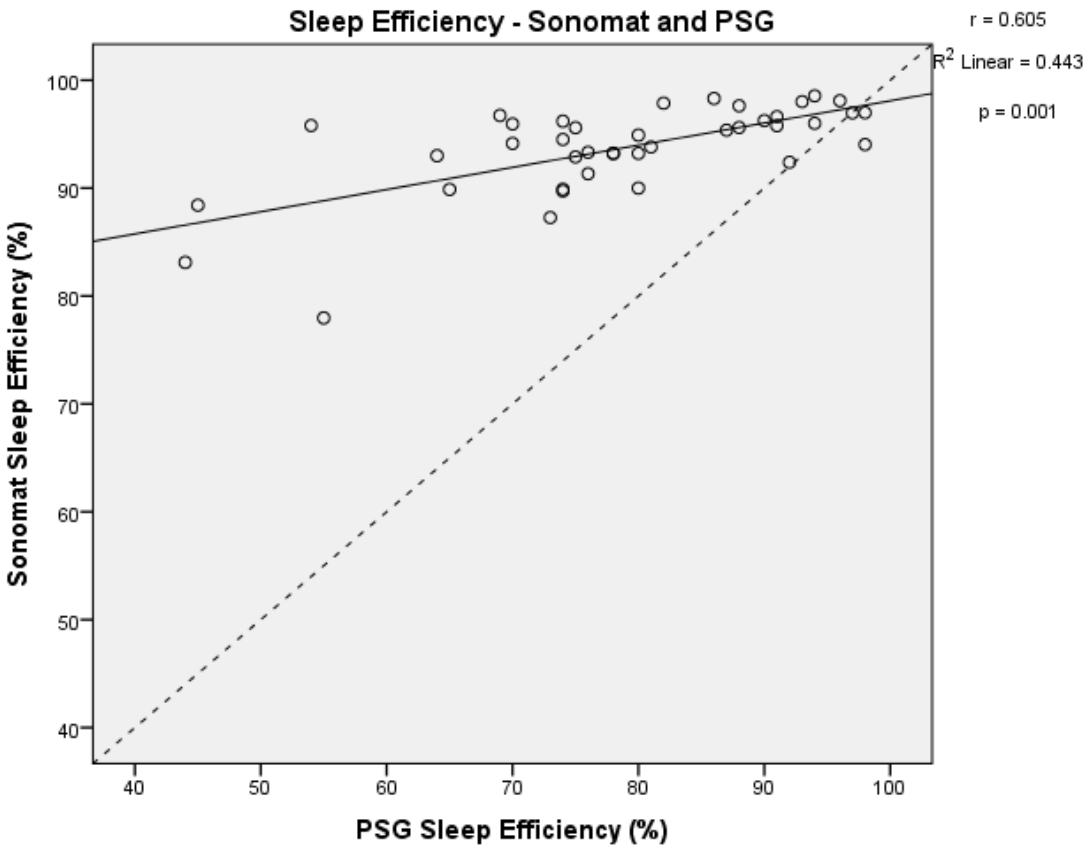

Figure 4.4 Sleep Efficiency – Sonomat and PSG

PSG: Polysomnography. Solid line: linear regression line. Dashed line: line of identity.

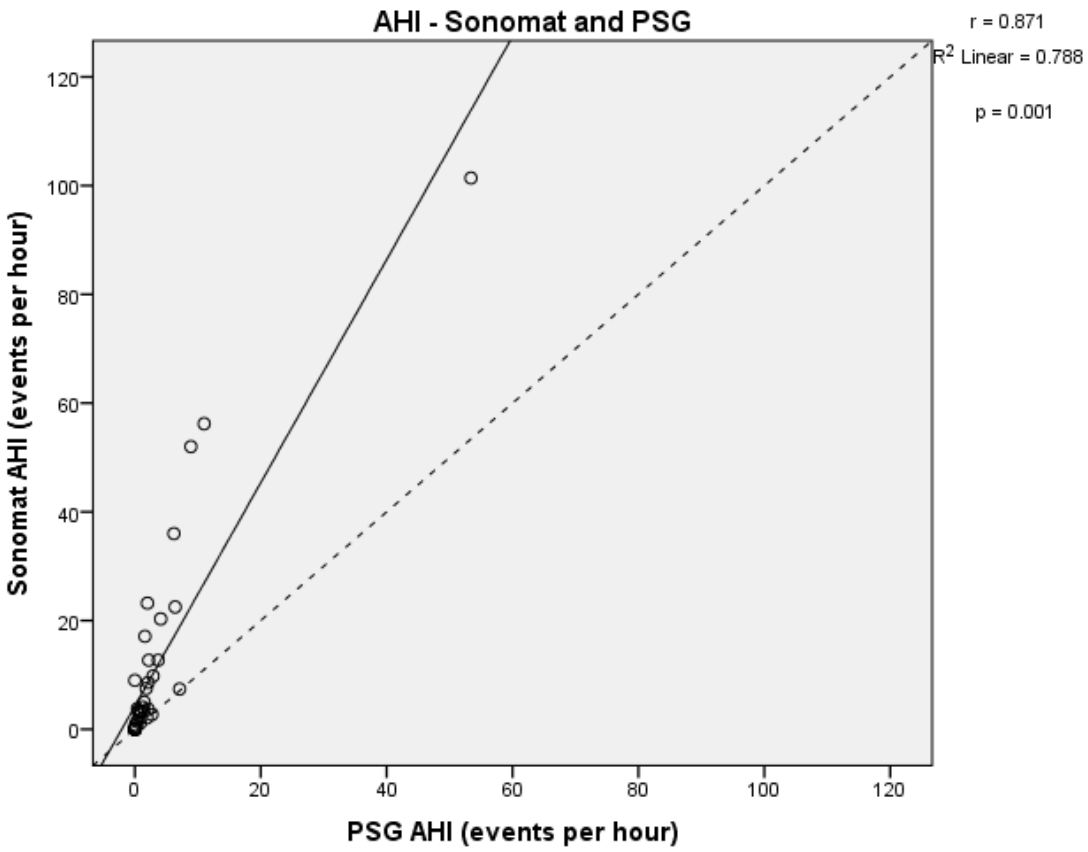

Figure 4.5 AHI – Sonomat and PSG

AHI: apnoea-hypopnoea index; PSG: polysomnography. Solid line: linear regression line. Dashed line: line of identity.

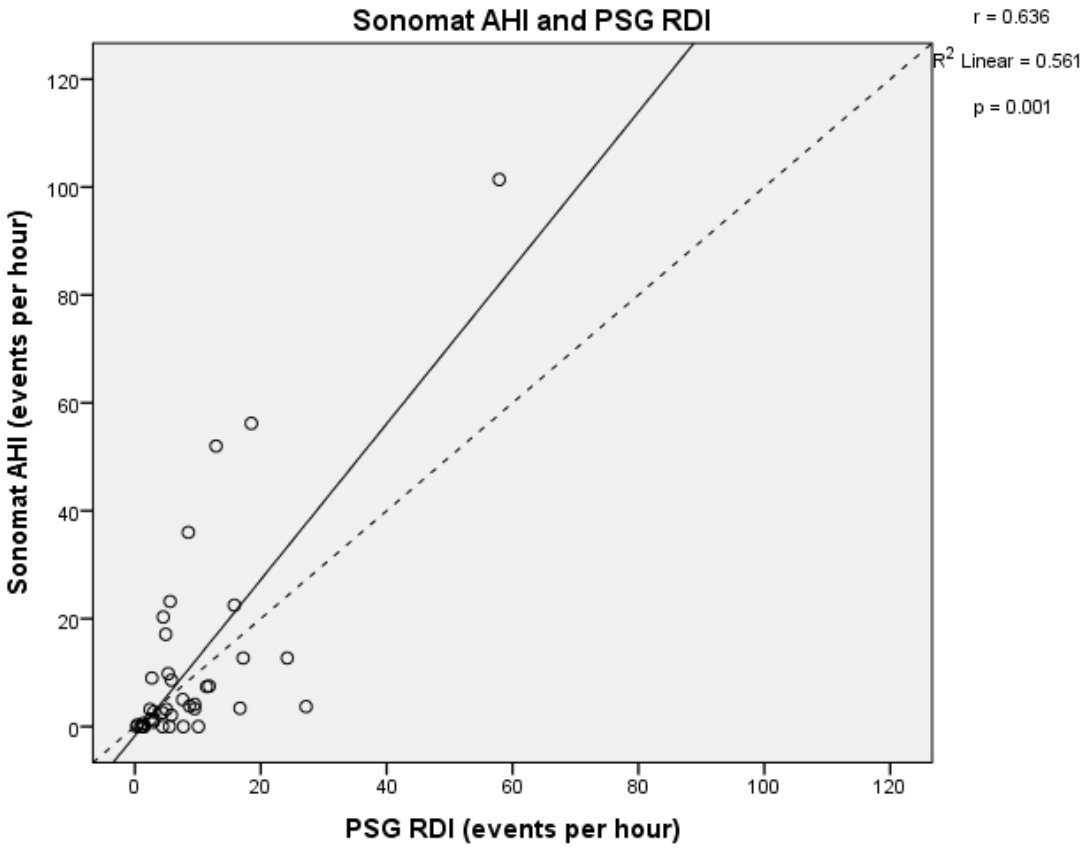

Figure 4.6 Sonomat AHI and PSG RDI

AHI: Apnoea-hypopnoea index; RDI: Respiratory disturbance index; PSG: polysomnography. Solid line: linear regression line. Dashed line: line of identity.

Lung Function and PSG Sleep Parameters

Using linear regression to assess influence of lung function (FEV_1 % predicted) on sleep parameters, only awake SpO_2 and nadir SpO_2 were positively correlated even weakly with FEV_1 % predicted ($p = 0.001$ and $p = 0.003$; $r^2 = 0.253$ and 0.186; respectively), see Figure 4.7 and Figure 4.8 below. Table 4.6 demonstrates the correlations of lung function with PSG parameters. For total RDI, total AHI, ODI and mean SpO_2 during

sleep time, there were no statistically significant correlations with FEV_1 % predicted (p = 0.293, 0.475, 0.564, 0.025; and r^2 = 0.032, 0.001, 0.001, 0.079; respectively).

Table 4.6 Correlation of Lung Function with PSG Parameters

Objective Sleep Variables	Correlation with lung function (FEV_1)		
	p-value	r	r^2
Arousal Index	0.743	-0.054	0.001
Sleep Efficiency	0.256	0.184	0.020
RDI	0.293	0.170	0.032
AHI	0.475	-0.116	0.001
ODI	0.564	-0.094	0.001
Awake SpO_2	0.001*	0.492	0.253
Mean SpO_2 during sleep	0.025	0.354	0.079
Nadir SpO_2	0.003*	0.455	0.186
Time spent with SpO_2 < 90 %	0.001*	-0.550	0.139

N = 40 subjects. FEV_1: Forced expiratory volume in 1 second; AHI: apnoea-hypopnoea index; RDI: respiratory disturbance index; ODI: oxygen disturbance index; SpO_2: oxygen saturation; *: significant correlation, using Spearman's calculation, correlation significant at the 0.05 level (2-tailed).

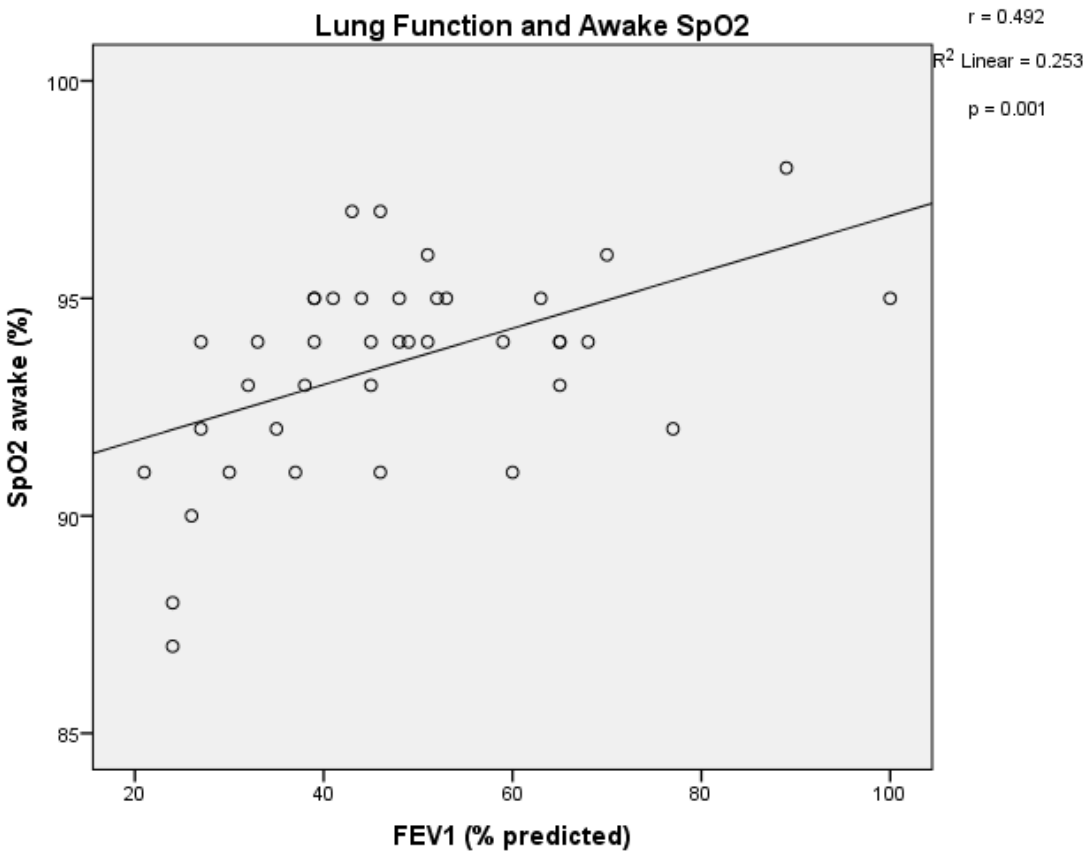

Figure 4.7 Lung Function and Awake SpO_2

SpO_2: oxygen saturation; FEV_1: forced expiratory volume in 1 second

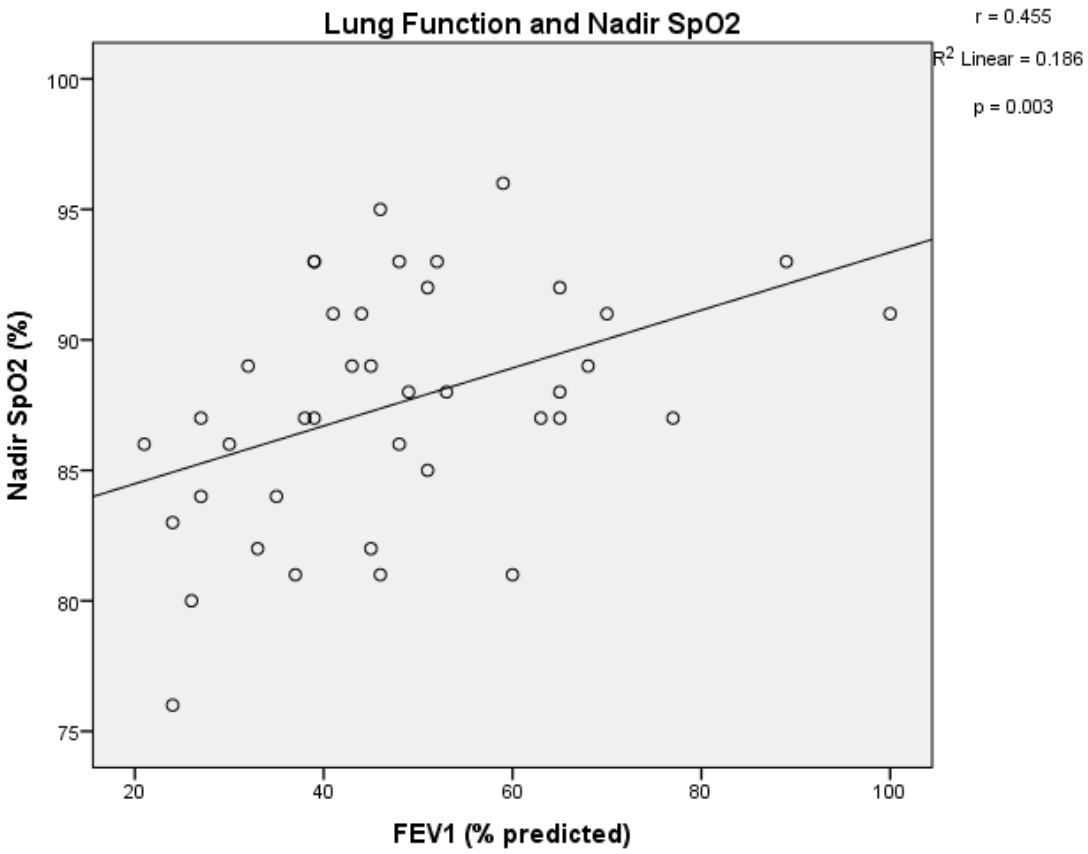

Figure 4.8 Lung Function and Nadir SpO_2

SpO_2: oxygen saturation; FEV_1: forced expiratory volume in 1 second

Lung Function and Sonomat Sleep Parameters

Using linear regression to assess the influence of lung function (FEV_1 % predicted) on Sonomat sleep parameters, it was found that there was no influence of FEV_1 on AHI, sleep efficiency nor % cough time (r^2 = 0.040, 0.002, 0.069, respectively). There was a weak significant correlation between % of sleep time spent with crackles and lung function (r^2 = 0.136), demonstrated in Figure 4.9. There was no correlation found between % time spent with cough and lung function, as shown in Table 4.7 below. These findings were similar to those we described above for the PSG parameters with total RDI and total AHI not significantly correlated with lung function (r^2 = 0.032 and

0.001; respectively). Awake SpO_2 and nadir SpO_2 were weakly positively correlated with FEV_1 % predicted (r^2 = 0.253 and 0.186; respectively), shown above in Table 4.6.

Table 4.7 Correlation of Lung Function and Sonomat Sleep Parameters

Sonomat Sleep Parameters	**Correlation with lung function (FEV_1)**		
	p-value	**r**	**r^2**
Crackles, % of total sleep time	0.032*	-0.339	0.136
Cough, % of total sleep time	0.058	-0.302	0.061

N = 40 subjects. FEV_1: forced expiratory volume in 1 second. *p-value significant < 0.05.

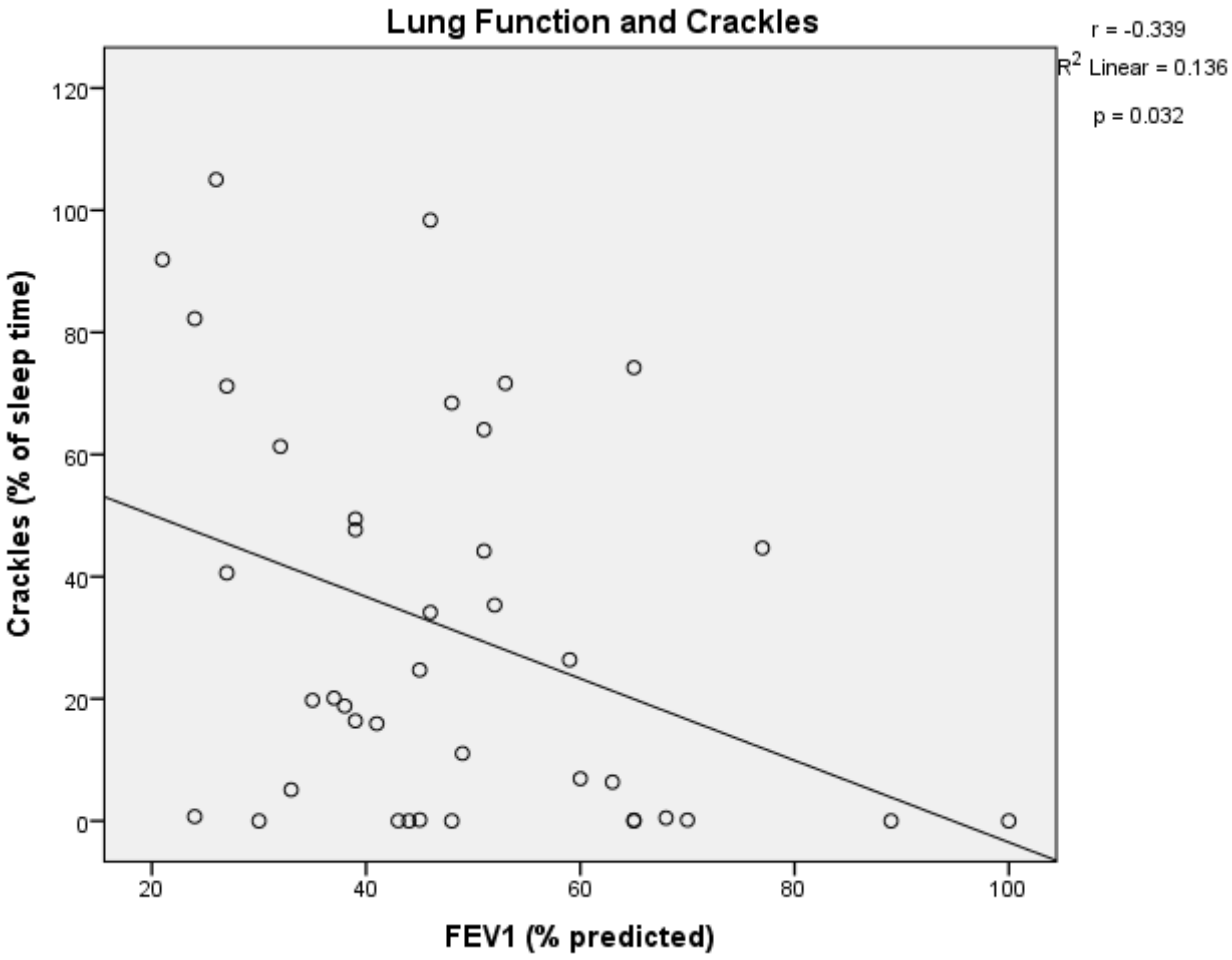

Figure 4.9 Lung Function and Percentage of Sleep Time with Crackles

FEV_1: Forced expiratory volume in 1 second.

Oxygen and PSG Parameters

SpO_2 during sleep time was statistically significantly correlated with awake SpO_2 ($p = 0.001$, $r^2 = 0.623$; shown in Figure 4.10) and nadir SpO_2 ($p = 0.001$, $r^2 = 0.565$; shown in Figure 4.11). There was no correlation between average SpO_2 during sleep and total RDI or total AI ($p = 0.137, 0.112$; and $r^2 = 0.027, 0.051$; respectively). However, there was a weak negative but statistically significant correlation between average SpO_2 during sleep time and total AHI ($p = 0.002$, $r^2 = -0.064$).

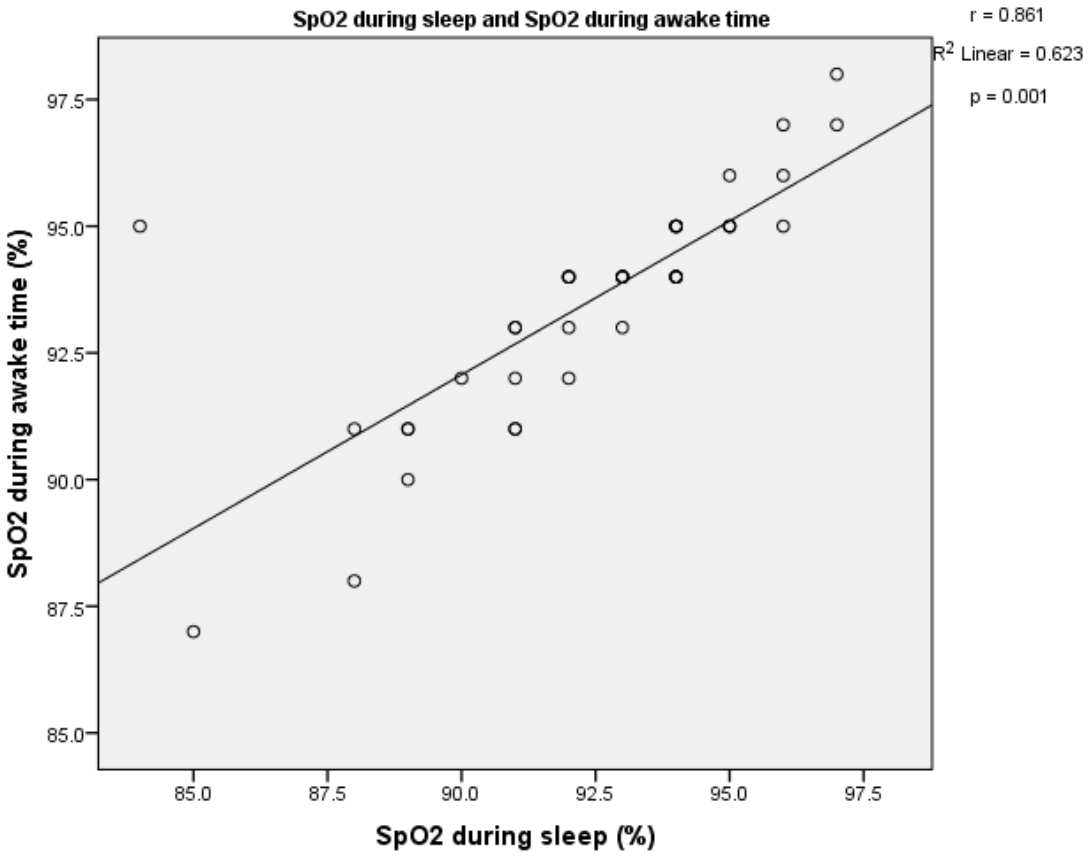

Figure 4.10 Oxygen Saturation during Sleep and Oxygen Saturation during Awake Time.

SpO_2: oxygen saturation.

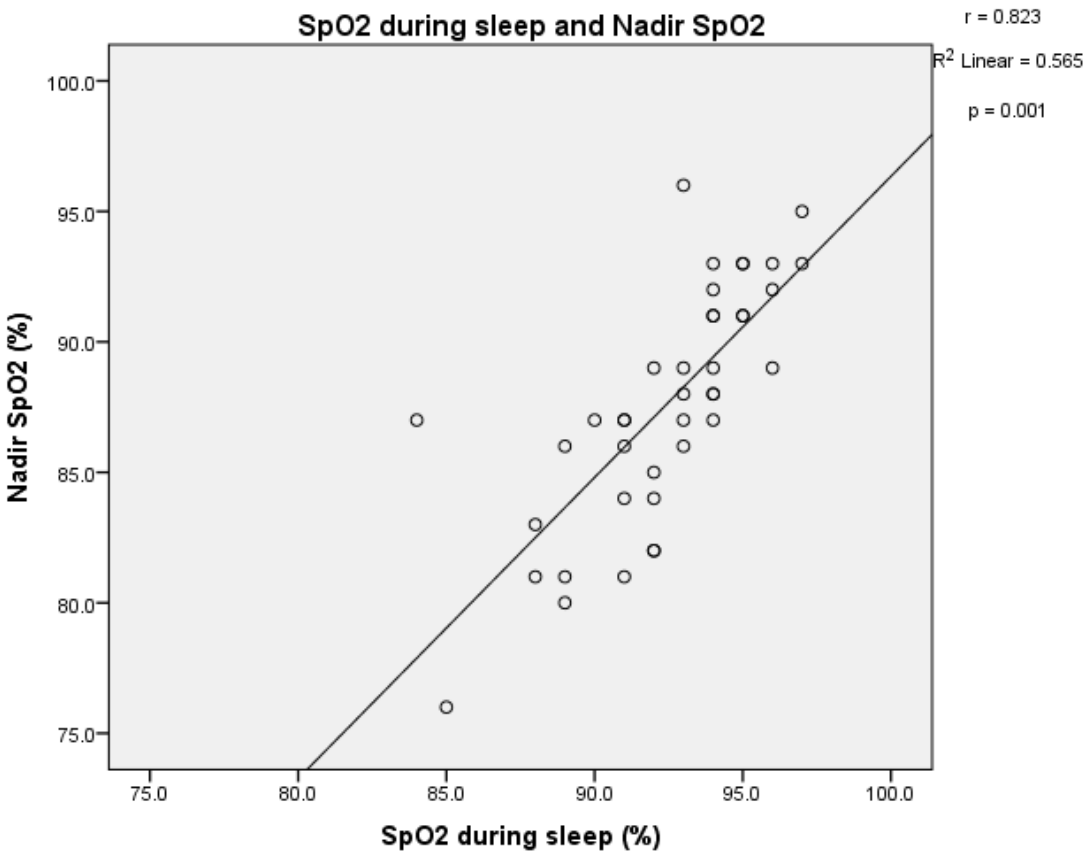

Figure 4.11 Oxygen Saturation during Sleep and Nadir Oxygen Saturation.

SpO_2: oxygen saturation.

Oxygen and Sonomat Parameters

Spearman's correlation to investigate the relationship between Sonomat results and oximetry from the PSG demonstrated a negative correlation between total AHI on the Sonomat with awake SpO_2 and nadir SpO_2 (r^2 = 0.180 and 0.257, respectively; p = 0.006 and 0.001, respectively). Time spent coughing was also inversely correlated with both awake SpO_2 and nadir SpO_2, see Table 4.8 and Figures 4.12 and 4.13 below.

Table 4.8 Correlations between PSG and Sonomat Oxygen Parameters

PSG parameter	Sonomat parameter	Spearman's Correlation	
		r^2 value	p value
Awake SpO_2	AHI	0.180	0.006*
	Sleep efficiency	0.051	NS
	% sleep time with cough	0.110	0.001*
	% sleep time with crackles	0.117	NS
	% sleep time with snores	0.016	NS
Nadir SpO_2	AHI	0.257	0.001*
	Sleep efficiency	0.042	NS
	% sleep time with cough	0.160	0.001*
	% sleep time with crackles	0.108	NS
	% sleep time with snores	0.011	NS

PSG: Polysomnogram; SpO_2: oxygen saturation; AHI: apnoea-hypopnoea index.

*Correlation is significant at 0.05 level (2-tailed).

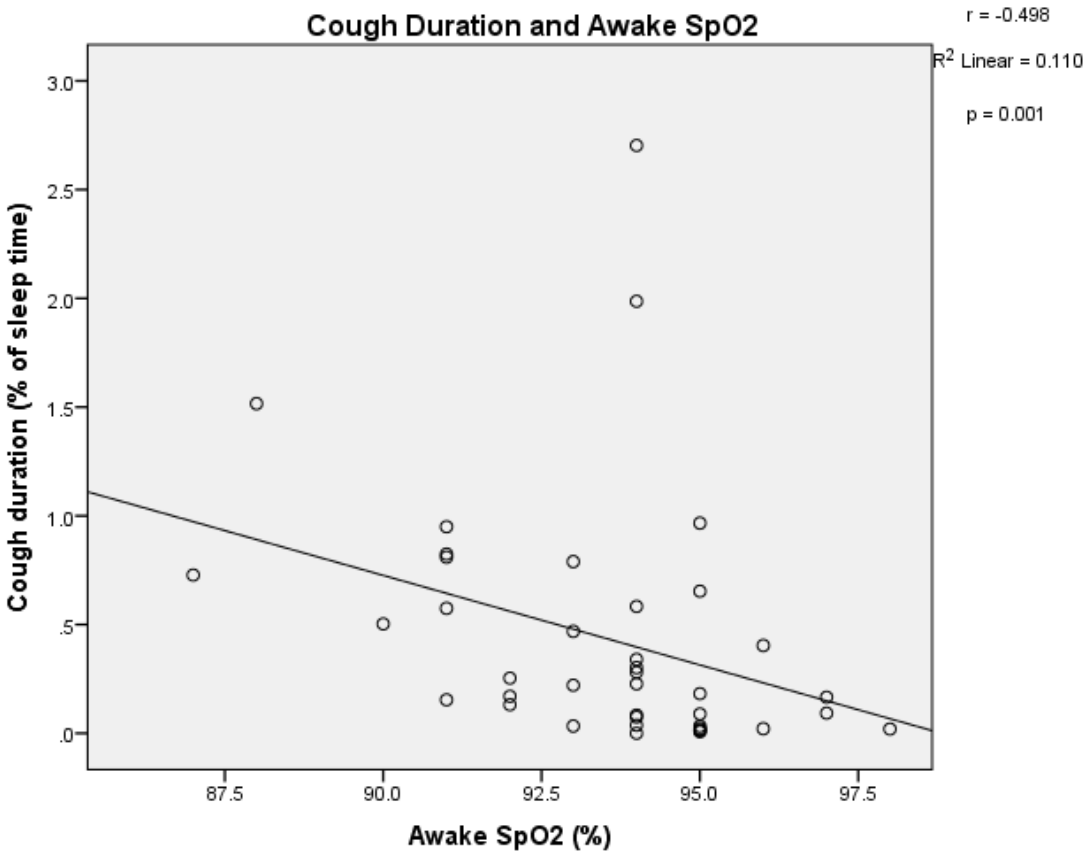

Figure 4.12 Cough Duration and Awake SpO_2

SpO_2: Oxygen saturation.

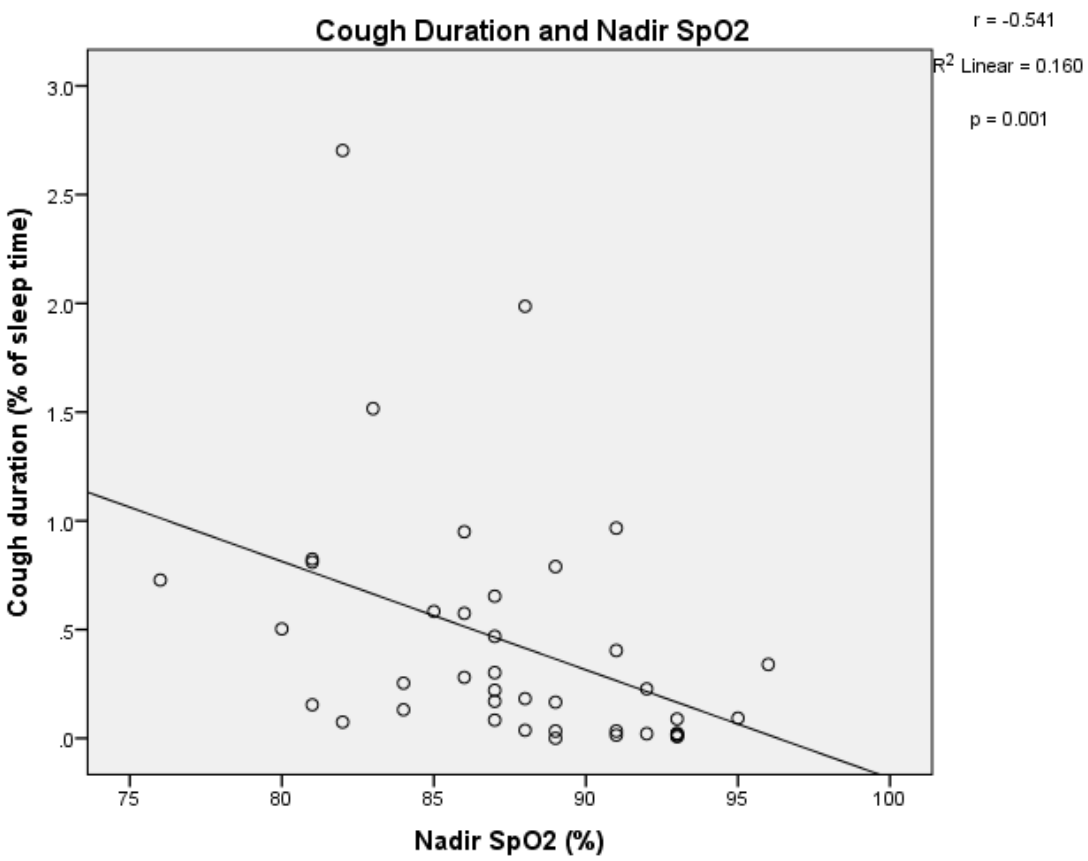

Figure 4.13 Cough Duration and Nadir SpO_2

SpO_2: oxygen saturation.

4.6 DISCUSSION

Polysomnography

In our cohort with mild through to severe CF lung disease, we found a low prevalence of sleep disordered breathing with RDI and AHI close to normal reference ranges (< 5 events per hour). Perin et al. found that there was an extremely low prevalence of obstructive sleep apnoea (3.9 %) observed in 51 clinically stable adult CF patients with

a mean FEV_1 % predicted of 57.7 ± 24.7 % (range 115 % to 19.5 % predicted) (Perin et al., 2012). Compared with the population studied by Perin et al., our subjects were older (mean age 33.8 vs 25.1 years in Perin et al.) and their lung function deficit was more severe (mean FEV_1 % predicted 47.9 vs 57.7 %) (Perin et al., 2012). In our study we found a higher prevalence of OSA of 12.5 % (where obstructive sleep apnoea was defined as AHI > 5 events per hour based on AASM 2007 Guidelines (Iber et al., 2007)), which may be due to an older and more compromised subject group in our study, compared with the Perin et al. study (Perin et al., 2012). Furthermore, if we use the definition of RDI > 5 events per hour for the diagnosis of at least mild obstructive sleep apnoea, the prevalence in our population was severely elevated at 57.5 %. However, other findings of our study are in keeping with those from Perin et al., 2012, who similarly found that awake SpO_2 correlated well with SpO_2 during sleep (Perin et al., 2012). In addition, we found that nadir SpO_2 correlated with SpO_2 during sleep.

In our study, we found a mean arousal index of 17.9 ± 8.3 events per hour which was higher than that reported by Perin et al. and de Castro-Silva et al. but similar to those reported by Bonnet and Arand (Bonnet and Arand, 2007, de Castro-Silva et al., 2009, Perin et al., 2012). Furthermore, Naqvi reported an increased arousal index of 28.3 ± 2.9 events per hour due to an increase in spontaneous arousals (Naqvi et al., 2008). This was not seen in our patient group. The mildly increased arousal index in our participants may be due to our subjects being older (mean age 33.8 years in our study vs 26.1 years in the Perin study) (Perin et al., 2012). There was no statistically significant correlation between age and AI in our subject group ($r^2 = 0.064$).

Reviewing sleep efficiency reported from previous papers, a reduced sleep efficiency of 71 % in 19 CF subjects with very severe lung disease (FEV_1 of 28 ± 7 % predicted), reduced SaO_2 during awake (mean 87 ± 6 %) and asleep (mean 84.4 ± 6.8 %) has been demonstrated (Dancey et al., 2002). In contrast, our population showed well preserved sleep efficiency at 78.7 ± 13.7 % and % of time spent in REM sleep. These differences between our findings and those above may be related to those subjects with poorer lung function experiencing chronic sleep restriction with sleep disruption and worse nocturnal hypoxaemia (Dancey et al., 2002).

In a small study from 30 years ago, with a total of 8 CF patients, Spier et al. reported a very low sleep efficiency of 58 % and reduced % of REM sleep (9.4%) in this group of adolescents and adults with severe lung disease secondary to CF (Spier et al., 1984). This contrasts with the findings of our study, where sleep efficiency and time spent in REM sleep were both within the lower limits of reference ranges. These differences may be due to the different study populations. Our subject group had more females, increased BMI and higher lung function than the 8 patients in Spier et al. (Spier et al., 1984). Spier further described that bouts of coughing often coincided with arousal and arousals sometimes occurred simultaneously with transient reductions in oxygen saturation measured by ear oximetry and reported as SaO_2 (Spier et al., 1984). However, they found that arousals more often occurred without drops in SaO_2 and drops in SaO_2 often did not result in arousals (Spier et al., 1984). Further, larger sample size populations may better address these issues.

Changes in sleep architecture as described by lower % REM sleep and reduced sleep efficiency / disruption have been shown to be correlated with the severity of lung

disease in the study by Naqvi et al. (Naqvi et al., 2008). This US study examined 24 children and adolescents with CF and found their sleep efficiency was within reference limits (at > 75 %) but lower than those of the 14 subjects in the control group at 85.6 % (Naqvi et al., 2008). The reported sleep efficiency in the CF group was similar to that in our group at 75.2 ± 2.5 % but they reported reduced % of REM sleep of 12.7 ± 1.5 % (Naqvi et al., 2008). In the Naqvi study, the degree of sleep disruption, as indicated by sleep efficiency, was correlated with severity of lung disease (Naqvi et al., 2008).

As discussed previously, EEG arousals have been shown to increase with increasing age (Bonnet and Arand, 2007). These authors found that the arousal index for the age group of 31 - 40 years, was 16.8 ± 6.2 events per hour (Bonnet and Arand, 2007). In our study of younger adult patients, with a mean age of 33.6 years, the arousal index was similar at 17.9 ± 8.3 events per hour (mean ± SD). The Naqvi study of children and adolescents looked at the arousal index and found a significantly higher arousal index, due to an increase in spontaneous arousals that was noted in CF patients (28.3 ± 2.9 events per hour vs 14.5 ± 1.4 events per hour; $p < 0.05$) (Naqvi et al., 2008). Cough related arousals are unable to be delineated from a spontaneous arousal by the PSG and hence, the Sonomat, a non-invasive recording device, may be useful to detect the causes of further abnormalities during sleep.

Night-time cough is thought to contribute to sleep fragmentation in patients with respiratory disease but few studies have looked at this specifically. Stokes performed an observational study of 9 patients with CF lung disease and found that cough in 3 of the patients resulted disruption of normal sleep stages and sleep cycles (Stokes et al., 1980). The contribution of cough resulting in sleep fragmentation contributing to

increased arousals and possible hypoxaemia was discussed by Perin but not accurately quantified in their study (Perin et al., 2012).

The presence of nocturnal hypoxaemia could potentially lead to arousal and sleep fragmentation / disruption. However, in our study we found that only nadir SpO_2 was weakly negatively correlated with arousal index and neither baseline SpO_2 nor mean SpO_2 during sleep time were correlated. Previous studies have looked at sleep disruption using actigraphy rather than PSGs (Amin et al., 2005, Jankelowitz et al., 2005). Jankelowitz et al. studied 20 stable CF patients and found that although these patients had disrupted sleep with a higher fragmentation index (calculated by summing the percentage of minutes spent moving with the % time spent in the immobility phase per minute) than controls (31.72 vs 18.04), CF patients and control subjects had similar sleep duration (7.52 hours vs 7.1 hours), sleep latency (12.75 min vs 13.85m min) and sleep efficiency (mean 85.2 % vs 85.4 %) (Jankelowitz et al., 2005).

Sonomat

The present study is the first study using the non-invasive device, the Sonomat, to investigate abnormalities breathing during sleep in adult subjects with CF. Norman et al. found a significant difference between sleep time based on the PSG and that from the Sonomat with PSG sleep time reported as 342.9 ± 10.6 minutes compared with Sonomat sleep time reported as 379.4 ± 10.0 minutes ($p < 0.001$) (Norman et al., 2014). This study showed that the total sleep time (TST) generated from Sonomat recordings overestimated the precise EEG derived TST by 37 minutes on average, but this difference was not sufficient to impact significantly on the AHI (Norman et al., 2014). These results differ from our own data with the TST derived from the Sonomat

overestimating the TST from the PSG by 62 minutes, on average. This may be due to the younger subjects in our study who may be awake but do not move sufficiently enough to activate the movement sensors on the Sonomat. Hence, we scored these periods as sleep but the precise EEG might score these periods as wakefulness based on the presence of alpha rhythms. Although, we found a moderately positive correlation of sleep efficiency between Sonomat and PSG ($r^2 = 0.443$), it is likely not to be accurate due to the above limitations of scoring TST using the Sonomat.

An advantage of the Sonomat, in this patient population, is its' ability to assess cough and lung sounds during sleep which are not recorded by the standard PSG. The interesting finding in this study was that the Sonomat can detect cough effectively but at the end of an admission, the range of cough duration during sleep was 0 to 734 seconds. Despite relatively little coughing, crackles were noted during 19.9 % of sleep time. The presence of crackles can suggest sputum retention and in keeping with those respiratory parameters that can be detected by the PSG (namely the awake SpO_2 and nadir SpO_2), respiratory function is compromised in these subjects with CF. With reduced lung function (FEV_1), the duration of crackles during sleep increases in keeping with poorer respiratory status. These additional parameters detected by the Sonomat can provide further supporting evidence that the respiratory status of subjects with CF can be affected both during the day time (as per lung function) and night time (based on crackles, cough and oxygen parameters).

It would be expected that the Sonomat AHI was correlated better with the PSG RDI rather than the PSG AHI due to the difference in scoring of events between the two

modalities. Arousals scored by the Sonomat by assessing changes in body movement sensors may be seen to be similar to arousals scored as respiratory effort related arousals (RERAs) in the PSG. We found weak correlation for sleep efficiency between the Sonomat and PSG (median 94.7 % vs 79.0 %; $r^2 = 0.443$) as well as a strong correlation between the Sonomat AHI and PSG AHI (median 3.4 events per hour vs 1.1 events per hour; $r^2 = 0.788$). Interestingly, in our study we found that PSG RDI was not as well correlated as the PSG AHI with Sonomat AHI, suggesting that the Sonomat may underestimate RERAs.

These results may be underpowered with our small sample size in this study. We found there was no influence of lung function on the AHI in both the Sonomat and PSG studies. It was described above, that only awake SpO_2 and nadir SpO_2 were positively correlated with lung function confirming that oximetry is a useful clinical tool in the assessment of subjects with lung disease. Further studies using the Sonomat along with oximetry will be valuable in the assessment of such patients in the long term. Limitations of this study included lack of control group, which may have allowed for a more direct comparison of our data to healthy or disease specific controls. In our small sample size, there was a wide range of AHI (0.0 to 53.4 events per hour). This low AHI may not be ideal for scoring of respiratory events from the Sonomat.

This study was a novel study using the non-invasive Sonomat device to characterise respiratory sounds in subjects with CF that are not detected by the conventional PSG. Extension of the single overnight study described in this chapter has been undertaken in Chapter 5 –Longitudinal data which details additional parameters useful in investigating the respiratory status of individuals with CF during sleep.

4.7 CONCLUSION

This study demonstrated that in these 40 CF adults (mean age of 33.8 years) with a range of lung disease severity, sleep parameters (sleep efficiency, sleep stages and arousal index) measured on polysomnography are similar to reported reference values in both CF and non-CF populations. We also demonstrated a high prevalence of mild (RDI > 5 events per hour) sleep disordered breathing (median RDI 5.6 events per hour), although the median AHI was within reference range (median AHI 1.1 events per hour). The main finding from the current study was that measurement of oximetry overnight can be correlated with lung function. Poorer lung function correlated with lower SpO_2 both awake as well as at the nadir SpO_2 but not the mean SpO_2 during sleep time. We found there was no correlation between poorer lung function and reduced sleep efficiency, AHI, RDI or AI in our study. A larger study to substantiate these findings and to further address the effects of sleep disruption and nocturnal hypoxaemia on quality of life and clinical outcomes is needed.

Based on the findings of the Sonomat alone, these adults with CF have good sleep efficiency (median of 94.7 %). AHI was reported to be within reference limits (median of 3.4 events per hour). Although, the percentage of sleep time with cough and snore is minimal, the presence of crackles at 19.9 % of sleep time is consistent with respiratory compromise in these subjects. The sleep efficiency of both the Sonomat and PSG is within reference values and correlates weakly ($r^2 = 0.443$). The overall AHI is similar between the Sonomat and PSG with a strong correlation demonstrated.

The Sonomat can be used to detect abnormalities in sleep and breathing using additional parameters, such as recording of coughs and crackles, not attainable with the PSG. In addition, lung function is not found to be correlated with AHI, sleep efficiency nor cough. Both the Sonomat and PSG showed there is no evidence of correlation between lung function and AHI in this current project. Hence, other parameters, such as crackles identified by the Sonomat, can be used to assess subject's respiratory status for adults with a wide range of lung function varying from normal to very severe airflow obstruction.

CHAPTER 5: OBJECTIVE SLEEP MEASUREMENTS IN ADULTS WITH CYSTIC FIBROSIS AND DETERIORATING LUNG DISEASE

5.1 INTRODUCTION

A number of measures can be used to assess nocturnal respiratory failure including overnight oximetry and polysomnography to assess sleep fragmentation, apnoeas and other respiratory events. Furthermore, with the use of the Sonomat, other aspects of sleep disordered breathing can be assessed. In particular, presence or absence of adventitial sounds which suggest pulmonary congestion and exacerbation of asthma or bronchiectasis can be assessed using the Sonomat over a period of time or at different time points.

Objective measurements of cough during pulmonary exacerbations have been studied previously by Smith et al. (Smith et al., 2006). These authors reported a reduction in cough rate with treatment but did not publish any longitudinal data to assess if cough rate increased again with future exacerbations and the effect of lung function deterioration on cough rate (Smith et al., 2006). In particular, these studies did not measure crackles or wheeze, only cough was recorded. In contrast to the study by Smith et al., fourteen CF children were studied by Hamutcu et al., and they found that the treatment of respiratory exacerbation improved neither the subjective (cough scores or visual analogue score) nor objective (ambulatory cough recording device – LR 100) measures of cough in CF children (Hamutcu et al., 2002, Smith et al., 2006). There have been no previous studies investigating the effect of deteriorating lung function on

overnight cough and other adventitial sounds, such as crackles, recorded by longitudinal studies.

In addition, if a patient is found to demonstrate nocturnal respiratory failure they can be offered treatment with non-invasive ventilation in an attempt to stabilise gas exchange function, especially as a bridge to lung transplantation (Hodson et al., 1991, Flight et al., 2012, Gozal, 1997, Milross et al., 2001a, Piper et al., 1992).

To perform repeated measures in the same individuals over time would then help to control for the individual variation in upper air physiology, and may allow delineation of a subtle relationship between lung function and SDB. Therefore, we undertook repeat studies in patients who had clinically deteriorated over a 1 to 3-year period to determine the severity of any changes in the night-time PSG and Sonomat recordings, and to compare the major clinical changes in functioning with the changes in PSG and Sonomat.

5.2 AIMS

The aims of this study included:

1. Assessment of nocturnal sleep disordered breathing in a subset of adults with CF after they have clinically deteriorated (shown by reduction in lung function, increased oxygen requirements or increased exacerbations) from their baseline study approximately 2 years earlier, to assess if SDB has deteriorated using PSG and Sonomat data.

2. Assessment of changes in measures of breathing disordered sleep using the additional respiratory parameters from the Sonomat.

5.3 HYPOTHESES

1. Nocturnal sleep disordered breathing is more severe in adults with CF after disease progression.
2. Deterioration of respiratory parameters during sleep detected by the PSG and the Sonomat (such as cough and crackles) correlates with deterioration in lung function in a subset of CF subjects.

5.4 METHODS

5.4.1 Subjects

Eight patients were enrolled who had clinical deterioration with: reductions in lung function (between 2 and 24 % drop in FEV_1 % predicted); frequent exacerbations (> 4 in the preceding 12 months); or worsening daytime hypoxaemia.

5.4.2 Measurements

Simultaneous overnight polysomnography and Sonomat use was repeated 1 to 3 years following the subject's first study, again at the end of an admission for an exacerbation.

The measurements used have been described in detail in Chapter 2 – Methods and further details discussed in Chapter 4.

5.4.3 Statistical Analyses

Using SPSS version 22 (SPSS Inc., IL, USA), the differences between the two groups at time baseline and the subsequent period were analysed using paired t-tests. Normally distributed data are presented as mean ± standard deviation (SD), and non-normally distributed data are presented as median and interquartile range (IQR).

5.5 RESULTS

Eight subjects were studied on 2 separate occasions. Demographic data is shown below in Table 5.1. There were 2 male subjects and 6 female subjects with a mean age of 26.5 years (SD ± 4.9 years). Overall, they were in the healthy weight range at baseline with a mean BMI of 21.0 kg/m^2 (SD ± 2.3 $kg.m^2$). Five subjects (63%) were homozygous for the F508del genotype. The mean FEV_1 (% predicted) had reduced from 45 % predicted initially to a mean of 33 % at the subsequent time period (SD ± 11.9), indicating overall a very severe obstructive ventilatory defect as per the American Thoracic Society and European Respiratory Society reference ranges (Pelligrino et al., 2005). FEV_1 % predicted and FVC % predicted both decreased from baseline to the subsequent study ($p = 0.002$ and $p = 0.003$, respectively). No other characteristics changed significantly from baseline to the subsequent study, except for awake SpO_2. On average, the subsequent sleep study was performed 1.8 years (range 325 to 1127 days) following the initial sleep study.

Table 5.1 Patient Characteristics in Longitudinal Study

Characteristics	Baseline	Subsequent	p - value
Male (n, %)	2, 25	-	
Age, years (mean ± SD) (range)	26.5 ± 4.9 (20 to 34)	28.5 ± 5.2	-
BMI, kg/m^2	21.0 ± 2.3	20.0 ± 2.0	0.184
Genotype, Homozygous F508del (n, %)	5, 63	-	
MucPSA (n, %)	4, 50	-	
FEV_1, % predicted	45.0 ± 11.9	33.0 ± 8.6	0.002*
FVC, % predicted	68.6 ± 13.9	53.1 ± 13.5	0.003*
Awake SpO_2, %	94.9 ± 2.0	92.9 ± 3.5	0.017*

N = 8 subjects. Data expressed as mean ± SD. BMI: body mass index; MucPSA: mucoid *Pseudomonas aeruginosa*; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; SpO_2: oxygen saturation. *p-value significant < 0.05.

Polysomnography

Data presented in Table 5.2 below, showed that sleep efficiency did not significantly change from baseline to the subsequent study (p = 0.827) and remained in the normal range (> 75 %). Although the arousal index did not significantly increase over time, it was above reference limits as per the reference ranges documented by Bonnet and Arand: for the age group between 21- 30 years, AI should be 10.8 ± 4.6 (Bonnet and Arand, 2007).

In this small group of CF subjects with deteriorating lung disease, mild sleep disordered breathing for the group was demonstrated with a mean respiratory disturbance index (RDI) rising from 6.9 events per hour at baseline (range: 0.3 to 18.5 events per hour) to 11.0 events per hour at the subsequent study (range: 1.2 to 21.7 events per hour; normal RDI is < 5 events per hour). Five out of the 8 subjects had a RDI greater than 5 events per hour.

Table 5.2 Baseline and Subsequent PSG Parameters in Longitudinal Study

Characteristic	Baseline	Subsequent	p-value
Sleep efficiency, %	78.3 ± 13.1	79.6 ± 11.7	0.827
NREM sleep, mins	280.7 ± 50.6	280.2 ± 34.7	0.984
REM sleep, mins	47.6 ± 27.5	65.7 ± 23.9	0.178
AI, events per hour	15.8 ± 6.5	20.0 ± 7.0	0.086
RDI, events per hour	6.9 ± 6.4	11.0 ± 7.4	0.085
AHI, events per hour	2.5 ± 4.1	5.1 ± 4.7	0.090
NREM AHI, events per hour	0.7 ± 1.2	1.2 ± 0.9	0.277
REM AHI, events per hour	11.7 ± 20.8	21.9 ± 17.3	0.133
Mean SpO_2 during sleep, %	93.4 ± 2.3	90.3 ± 4.0	0.016*
Nadir SpO_2, %	89.0 ± 4.6	82.8 ± 8.9	0.065
Oxygen desaturation during sleep, %	1.4 ± 1.9	4.0 ± 2.1	0.01*

N = 8 subjects. Data expressed as mean ± SD. Mins: minutes; NREM: non-rapid eye movement sleep; REM: rapid eye movement sleep; AI: arousal index (normal < 11 events per hour) (Bonnet and Arand, 2007); RDI: Respiratory disturbance index (normal < 5 events per hour); AHI: Apnoea-hypopnoea index (normal < 5 events per hour); SpO_2: oxygen saturation. * p-value significant at < 0.05.

Mean SpO_2 during sleep was mildly reduced initially at 93.4 % dropping significantly to 90.3 % at the repeat study (p = 0.016). It was also shown that oxygen desaturation during sleep significantly increased between the two studies from 1.4 to 4.0 % (p = 0.01). Although, nadir SpO_2 was low and reduced further on the subsequent study, it was not statistically significant (p = 0.065).

The longitudinal data for individual subjects (n = 8) are shown for the sleep parameters of: arousal index, RDI and oxygen desaturation in Figures 5.1 to 5.3. Shown in Figure 5.1, one subject (subject no. 3) had a mild reduction in AI over time but for all other subjects AI increased, although it was not statistically significant.

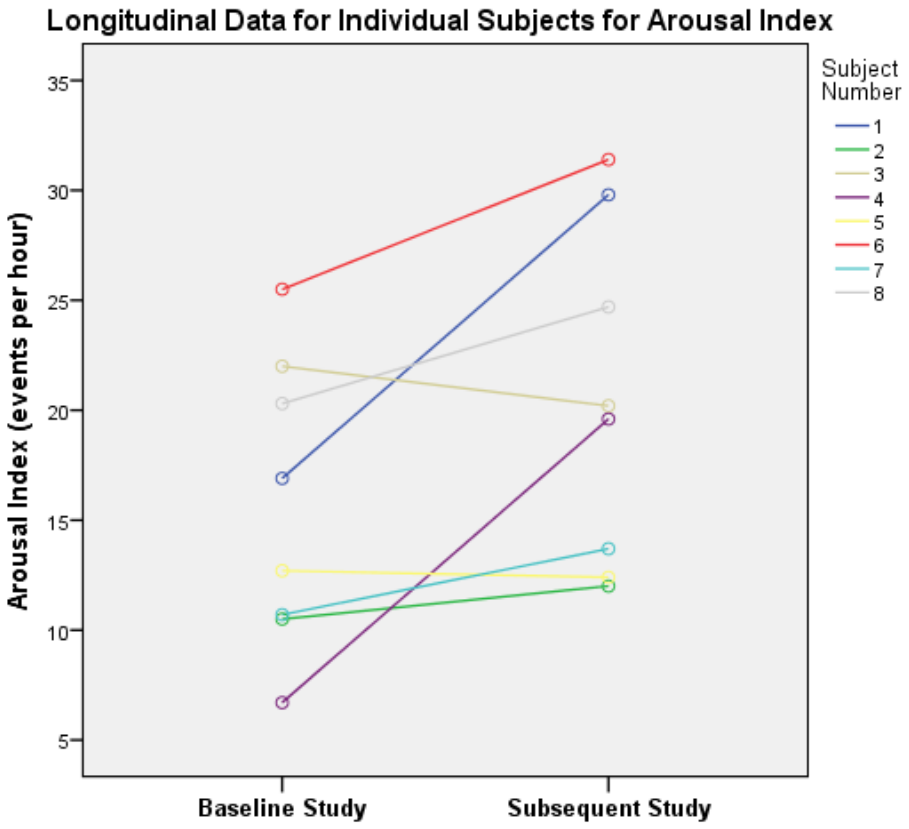

Figure 5.1 Arousal Index shown at Baseline and at Subsequent Study.

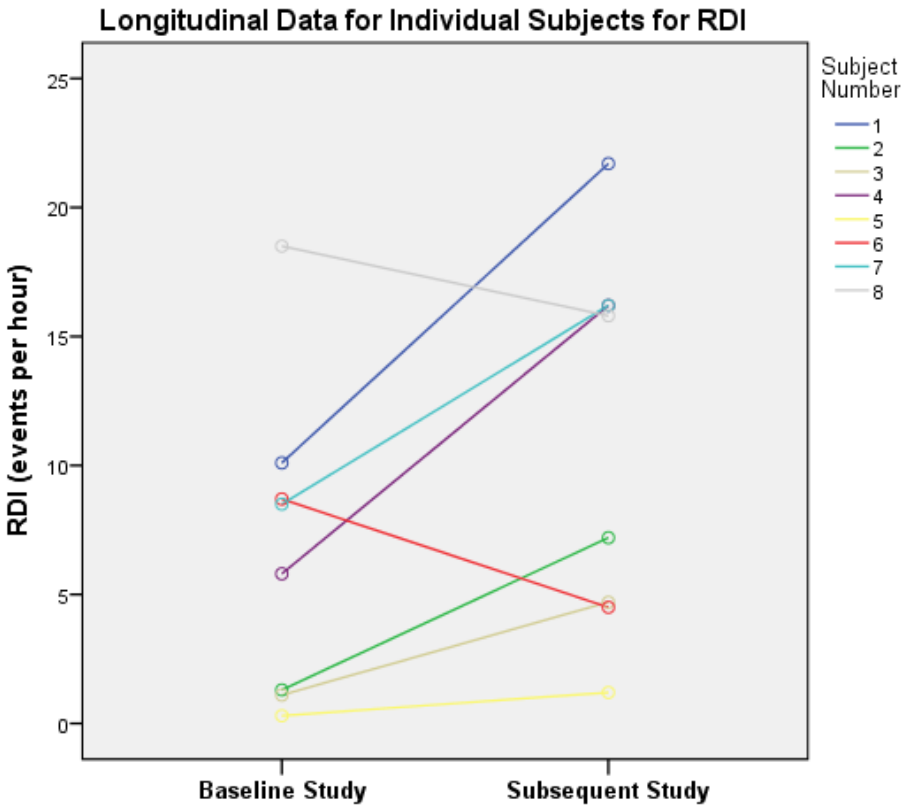

Figure 5.2 Respiratory Disturbance Index (RDI) at Baseline and Subsequent Study

The above figure, Figure 5.2, demonstrated the change in RDI between the two-time periods with 2 subjects (subject no. 6 and no. 8) showing a reduction in RDI over time. The numbers remain small and were not statistically significant.

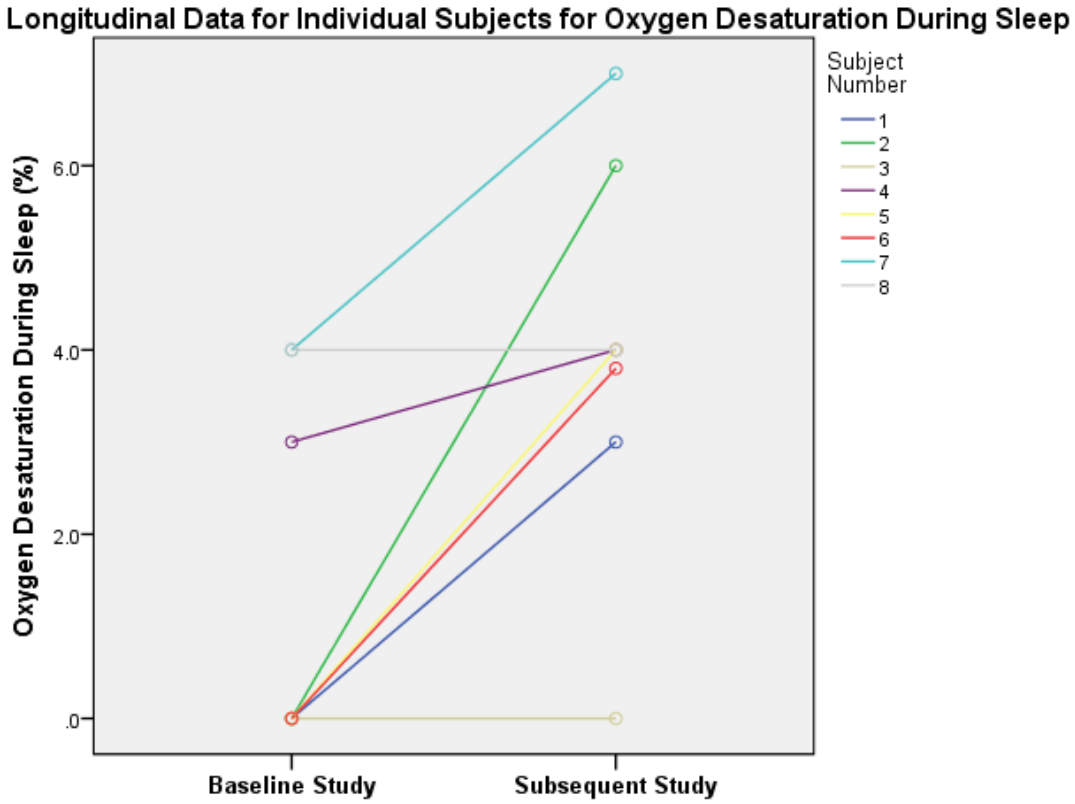

Figure 5.3 Oxygen Desaturation during Sleep at Baseline and Subsequent Study

As shown above in Figure 5.3, in CF subjects with deteriorating lung function, oxygen desaturation worsened over time for all except 2 subjects (subject no. 3 and no. 8) which remained stable from baseline.

Sonomat

Further baseline data for Sonomat results are shown in Table 5.3.

Table 5.3 Demographic Data for Individual Subjects at Baseline Study

Subject	Age (yrs), Gender	FEV_1 (% pred.)	Genotype	Cough, % sleep time	Crackles, % sleep time	Snores, % sleep time	Sonomat AHI, events per hour
1	34, F	45	F508del/UNK	0.79	24.7	15.6	0.0
2	29, F	39	F508del/F508del	0.03	16.4	0.1	0.7
3	20, F	46	1898+IG>A/UNK	0.12	34.2	61.1	0.1
4	25, M	68	F508del/F508del	0.09	0	1.3	1.6
5	32, F	52	F508del/Other	0.09	35.2	2.0	0.0
6	21, M	27	F508del/F508del	0.27	40.4	4.0	0.7
7	26, F	38	F508del/F508del	0.22	18.8	0.2	1.0
8	25, F	45	F508del/F508del	2.48	0.2	24.3	0.0

N = 8 subjects. F: female; M: male; FEV_1: forced expiratory volume in 1 second; UNK: unknown genotype; AHI: apnoea-hypopnoea index.

Sleep efficiency based on quiescent time was shown to be normal (mean of > 92 %) both at baseline and at the subsequent study. Of note, in this small group of CF subjects with severe lung disease, there was no evidence of sleep disordered breathing with a mean apnoea-hypopnoea index (AHI) of 2.1 events per hour at the subsequent study (normal AHI is defined as < 5 events per hour), shown in Table 5.4.

Table 5.4 Sonomat Sleep Characteristics – Baseline to Subsequent Study

Characteristic	Baseline	Subsequent	p-value
Sleep efficiency, %	92.7 ± 6.2	93.2 ± 5.3	NS
AHI, events per hour	0.5 ± 0.6	2.1 ± 1.7	0.022
Cough, % of sleep time	0.2 (0.6)	0.2 (0.4)	NS
Total sleep time with cough, seconds	36.0 (136.3)	42.0 (100.5)	NS
Coughs, per hour	3.6 (8.5)	2.6 (7.8)	NS
Cough, total number of episodes of:			
1 cough	0.0 (7.0)	0.0 (0.0)	NS
2 - 5 coughs	9.5 (51.3)	15.0 (47.8)	NS
> 5 coughs	0.5 (2.5)	2.0 (9.3)	NS
Crackles, % of sleep time	21.8 (30.7)	81.7 (24.9)	0.001
Snores, % of sleep time	3.0 (21.6)	5.3 (11.6)	NS

N = 8 subjects. Data expressed as: mean ± SD for normally distributed data or median (IQR) for non-normally distributed data. AHI: apnoea-hypopnoea index; NS: not statistically significant. Correlation significant at the 0.05 level (2-tailed).

In patients with deteriorating lung function, there was a marked increase in sleep time spent with crackles. There was an overall minor increase in AHI between the two studies, however, it remained within the normal reference range (normal < 5 events per

hour). There was a trend to an increase which was not significant in coughs but not snores, Table 5.4.

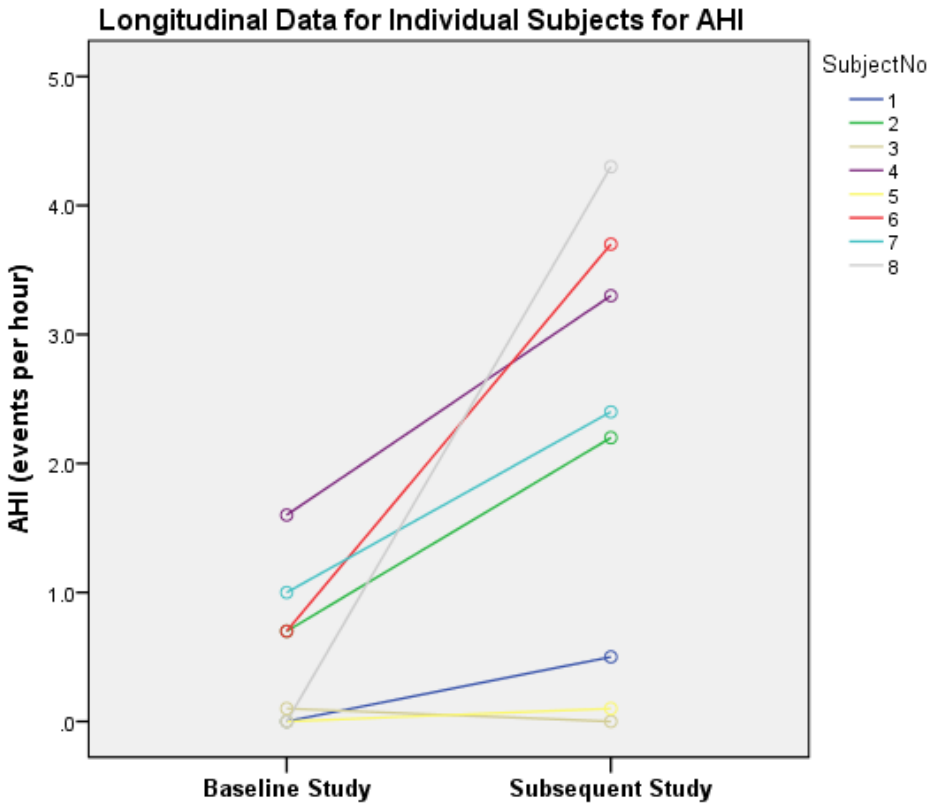

Figure 5.4 Longitudinal AHI Data for Sonomat

Subjects: n = 8. AHI: apnoea-hypopnoea index.

Figure 5.4 demonstrated the individual variability between the two-time points with some subjects (subject numbers 1, 3 and 5) showing little difference in AHI between the two Sonomat studies. Whereas, subjects 6 and 8 showed larger differences in AHI between the two sleep studies, but none of clinical significance (all < 5.0 events/hour).

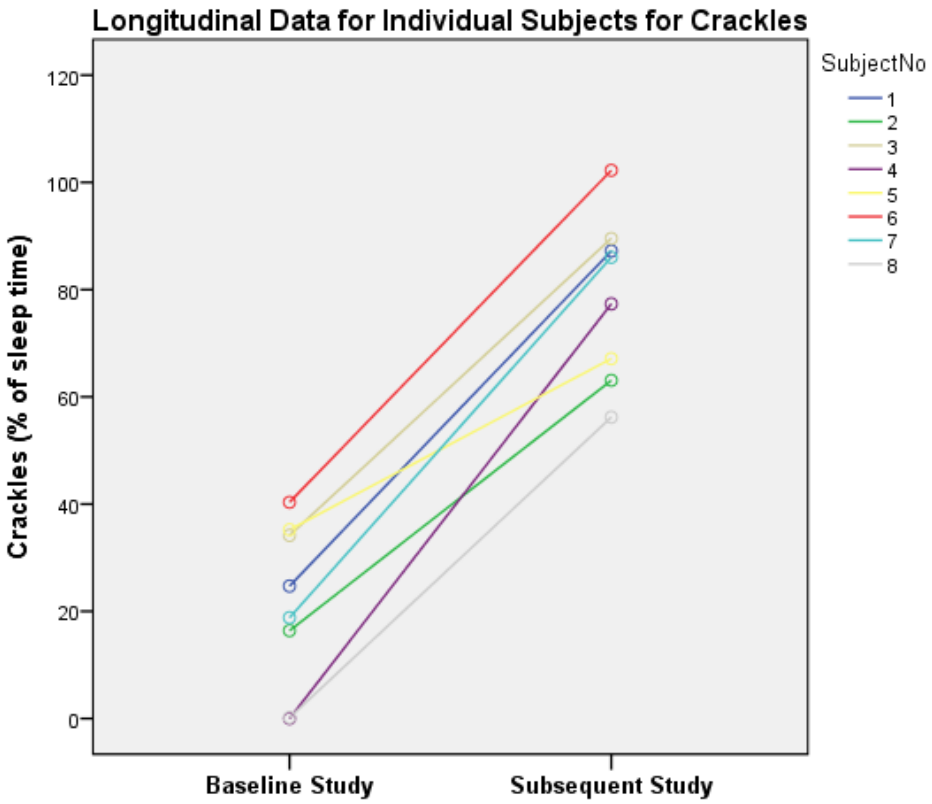

Figure 5.5 Longitudinal Data for Crackles from Sonomat

Subjects: n = 8.

In the figure above, all subjects increased in the percentage of time spent with crackles ($p = 0.001$).

5.6 Discussion

Polysomnography

We found that SpO_2 was reduced over time with more desaturation events, but interestingly this was not reflected in deterioration of some of the indicators of nocturnal sleep disordered breathing (arousal index, RDI and AHI).

Our study demonstrated the arousal index was above the reference limits proposed by Bonnet and Arand but did not change significantly over time which was an unexpected result (Bonnet and Arand, 2007). Although the arousal index was above reference limits, the sleep efficiency was normal (mean 79.6 %) even at the subsequent study in our small group. This suggests that although the subjects are roused during the night it does not impact on the overall sleep duration / efficiency, which may be due to their younger age compared with the older age population of OSA subjects from where the reference values are derived or may be due to the fact that the subjects were studied immediately post treatment of an exacerbation. Previous studies by Boselli et al. and Mathur and Douglas have shown significant correlation between age and AI in normal subjects (Boselli et al., 1998, Mathur and Douglas, 1995).

An earlier study performed by de Castro et al. of 40 CF subjects and 20 control subjects found that PSG can reveal the occasional subject with OSA (n = 3, AHI reported at 8 to 11 events per hour) but no major sleep alterations other than oxygen desaturation in clinically stable CF patients with and without significant CF lung disease (mean FEV_1 65.3 % and 99.8 % predicted, respectively) (de Castro-Silva et al., 2009). In our study of 8 subjects, we found 3 of the subjects fulfilled the criteria of mild to moderate OSA (where AHI > 5 events per hour; range 7.3 to 13.8 at the subsequent sleep study). If we look at RDI instead, there was an increase in sleep disordered breathing with mean RDI of 11.0 events per hour at the subsequent study. The inclusion of RERAs as part of the definition of RDI suggests these subjects have arousals due to respiratory efforts but as this does not reach the criteria for hypopnoea is not included as part of the AHI definition. It could be possible that the subtle RERAs are due to the effects of lung disease / poorer ventilation that affect the overall subject's breathing during sleep.

Small alterations in gas exchange and ventilation that normally occur during sleep can be exaggerated in patients with CF lung disease resulting in significant oxygen desaturation which may be due to hypoventilation or ventilation/perfusion mismatching (Milross et al., 2004).

As expected, in our study, mean daytime SpO_2 (94.9 ± 2.0 % reduced to 92.9 ± 3.5%) and mean night-time SpO_2 (93.4 ± 2.3 % reduced to 90.3 ± 4.0 %) deteriorated significantly over the 2-year period. Milross et al. studied 32 CF subjects with moderate to severe lung disease and found similarly mean awake SaO_2 was 93 % and nocturnal SaO_2 was 90 % (Milross et al., 2001b). Bradley et al. reported a mean nadir SpO_2 of 82 ± 8 % in 14 younger subjects with CF which is similar to our findings in the repeat PSG study of a nadir SpO_2 of 82.8 ± 8.9 % (Bradley et al., 1999). These changes in oximetry measurements may be due to deteriorating lung function leading to an overall lower baseline SaO_2 with these awake saturations being near or on the start of the steep portion of the oxyhaemoglobin-dissociation curve, as previously described by Francis in 1980 (Francis et al., 1980). Hence, a small fall in SaO_2 would result in greater falls in PaO_2 over the time period. This may also impact on the measurement of AHI, as AHI is scored based on reductions in SaO_2. The issue of posture may also contribute to these changes. In subjects with CF, the supine position is associated with increased perfusion of the apical, likely more scarred, and poorly ventilated zones, thereby worsening ventilation and perfusion matching (Wood et al., 1976).

Interestingly, in our study we found that sleep architecture and sleep efficiency did not change over time as expected. In the study by Milross et al., they too found that sleep efficiency (mean 87 ± 6 %) and sleep architecture were not abnormal in their CF

subjects with moderate to severe lung disease (Milross et al., 2001b). Likewise, Jankelowitz et al. (2005) demonstrated that using actigraphy sleep duration and sleep efficiency (mean 85.2 ± 6.15 %) were within normal limits in CF patients with moderate CF lung disease but showed increased fragmentation (Jankelowitz et al., 2005).

These results may be due to the small subject numbers which may reduce the size of effect but it also raises the question that different parameters may be more useful to assess respiratory status during sleep in these subjects. Using the Sonomat to analyse adventitial sounds during the night may provide further information which can assist clinicians in making decisions regarding treatment of abnormal sleep parameters.

To our knowledge, this is the first study to investigate the longitudinal effects on sleep using PSG in CF patients with deteriorating lung function of up to a 3-year period of review. However, these results should be interpreted with caution due to the small subject number making it difficult to draw firm conclusions. The analyses of paired data were utilised in an attempt to minimise this limitation. However, larger sample sizes are warranted to further evaluate the abnormalities of sleep over a longitudinal period to detect a significant effect.

Sonomat

This was the first study to use a non-invasive sleep monitoring device, the Sonomat, in CF subjects to assess abnormalities during sleep longitudinally. The Sonomat is useful in detecting adventitial sounds which provide additional data to analyse the sleep abnormalities in adults with CF. It was hypothesised that nocturnal cough and crackles would worsen over time in these CF subjects with deteriorating lung function.

Interestingly, coughs did not increase but the presence of crackles increased substantially in this study. This may be due to suppression of cough during sleep as reported previously by a number of authors including Krajnik et al., Power et al., and Smith et al., 2008 (Krajnik et al., 2010, Power et al., 1984, Smith and Woodcock, 2008). Hence, a potential limitation in our study may be insufficient awake data to analyse the cough duration prior to sleep time.

One of the seminal papers investigating the suppression of cough during sleep presented findings indicating that cough and smooth airway muscle constriction in response to bronchopulmonary irritants do not occur in sleeping tracheotomised dogs in the absence of arousal, and that arousal responses to such stimuli are depressed in REM sleep (Sullivan et al., 1979). In patients with chronic cough, Krajnik et al. found that at night the median time spent coughing was 3 seconds per hour compared with daytime cough of 20 seconds per hour in a small study of 13 patients (Krajnik et al., 2010). Power et al. reported that of 10 patients with nocturnal cough, only one patient coughed during REM sleep and none coughed during Stage 3 or 4 sleep (Power et al., 1984). They also found no correlation between cough and sleep disordered breathing (Power et al., 1984), but were not able to measure other adventitial sounds such as crackles or wheezes.

Our results may also be influenced by the fact that both studies were performed when the subjects were stable, that is, they did not have a pulmonary exacerbation at the time of the study. Although the adults with CF had exhibited a deterioration in FEV_1 over the 2-year follow-up, there may have been less difference between the recordings when relatively well, with differences only exhibited when the adults were unwell. Hence,

nocturnal cough might not be evident unless increased mucus clearance is needed to expel increased sputum volume from the airways. In a study of 133 patients with a respiratory illness and use of nocturnal long-term recording of respiratory sounds, Gross et al. found that following therapeutic treatment of bronchial obstruction, there was a clear reduction in cough and wheezing events (Gross et al., 2007).

Smith et al. used ambulatory sound recordings on patients with CF at the beginning and end of a hospital admission for the management of a pulmonary exacerbation. Median cough rate during the day on admission was 21.2 cough seconds per hour and by discharge, it was 9.0 cough seconds per hour. During the night, the cough rate was much lower with median cough rate at night on admission of 4.8 cough seconds per hour and on discharge, median cough rate of 1.5 cough seconds per hour (Smith et al., 2006). There was a significant decrease in cough rate with the treatment of a pulmonary exacerbation both during the day (median fall of 51.3% (IQR 32.2 – 77.5)) and night (median fall of 72.2% (IQR 28.6 – 90.1)) (Smith et al., 2006). It was postulated that the coughing that occurs overnight with exacerbations may be a better reflection of airway inflammation than daytime coughing as overnight the subjects are less likely to be exposed to environmental irritants or changes in temperature than during the day (Smith et al., 2006). Similar to the Smith et al. study, in our study, there was minimal coughs per hour of sleep with a median of 3.6 per hour at initial study and 2.6 coughs per hour at subsequent study (Smith et al., 2006). Noting again, our study was performed during a period of non-exacerbation where cough may be minimal.

In our small group of CF subjects re-studied after the development of more severe lung disease, there was no evidence of sleep disordered breathing with mean apnoea-hypopnoea index (AHI) of 2.1 events per hour (normal AHI < 5 events per hour).

However, the AHI did significantly increase over the time period from the initial study to the subsequent study. This may be in part due to the technical limitation of the Sonomat with simultaneous scoring of crackles, hypopnoea/apnoeas and other sounds in the same time period (epoch) making it difficult to score each respiratory event individually. The presence of cough or crackles in both the audio and movement sensors can occasionally override the body movement sensor tracings alone which is used to classify the apnoeas or hypopnoeas.

Adding further information onto the standard PSG may be useful in CF patients. If it is noted over time that nocturnal crackles (indicative of mucus retention) are increasing on home-based monitoring, treatment might be directed to increase mucus clearance with increased physiotherapy regimens to prevent a pulmonary exacerbation. Furthermore, using the Sonomat or another non-invasive device, such as a recording electronic stethoscope, during the daytime may also be useful to detect and quantify crackles indicating reduced mucus clearance. These methods may in fact be more cost effective than overnight monitoring using a PSG. However, the duration and timing of daytime recordings has not been previously validated and this would need to be performed prior to establishing a threshold for the presence of crackles or other adventitial sounds.

Limitations to this study included the small sample size which restricts the generalisability of these measurements. With larger sample sizes, the effect of the presence of cough, crackles and snores during sleep may change. Interestingly, wheeze was seldom recorded overnight in these subjects. As discussed above, the simultaneous presence of multiple sounds and respiratory events have made it difficult to score each

individual event using the Sonomat. Hence, the Sonomat may sometimes underestimate the presence of sleep disordered breathing including apnoeas or hypopnoeas due to the presence of cough or crackles overriding the audio sound above the changes in body movement data tracings. However, future studies developing automated algorithms using the Sonomat may assist in overcoming these issues and are currently underway.

5.7 CONCLUSION

Our longitudinal study of CF subjects with severe CF lung disease demonstrated that sleep efficiency and sleep architecture were within reference values and did not change significantly over time. However, there was a trend to an increase in RDI and AI over this period with a higher prevalence than was expected in sleep disordered breathing. As expected with deterioration in lung function, overall oxygenation during sleep was reduced at both the baseline and further reduced at the subsequent study. However, only the oxygen desaturation showed a statistically significant increase between the two study periods. The above results warrant further validation with larger paired studies to analyse sleep abnormalities that occur in CF subjects with a range of lung function severity.

In this subset of patients with severe CF lung disease, sleep efficiency did not between two periods of review. The time spent with crackles during the night increased significantly over the course of 1-3 years (from median of 21.8 to 81.7 % of total sleep time). Interestingly, the time spent coughing or snoring did not change significantly over the course of this time period. Larger longitudinal studies with increased subject

sample size and more frequent testing would aid in determining if the presence of or an increase in crackles suggests worsening respiratory function or an exacerbation of disease and the need to act earlier to treat subclinical pulmonary exacerbations to minimise deterioration.

CHAPTER 6: SLEEP QUALITY AND QUALITY OF LIFE IN ADULTS WITH CYSTIC FIBROSIS

6.1 INTRODUCTION

As outlined in Chapter 1, Quality of life (QoL) reflects an individual's subjective evaluation of his or her daily functioning and well-being. QoL measures incorporate several core domains, such as physical functioning and symptoms, psychological and emotional state, and perception of ability to perform activities of daily living. The QoL questionnaires can provide a formal, reproducible and structured method of establishing the patient's perspective as to the effectiveness of their current or previous therapies.

In the CF group, it is known that objective clinical measures, such as forced expiratory volume in 1 second (FEV_1) and six-minute walk test (6MWT), are useful in assessing objective effectiveness of therapy, but do not relate closely to measures of QoL including sleep QoL (Fauroux et al., 2012). Hence, health related quality of life is an important outcome measure in CF (Abbott et al., 2011). Previous studies have looked at both generic QoL measures as well as disease-specific QoL measures (CF QoL and CFQ-R) and have reported that the disease-specific measures can be used in different applications including detecting transient changes in health status as well as looking at longitudinal changes that occur in adults with CF due to progression of disease (Gee et al., 2000, Modi and Quittner, 2003, Quittner et al., 2012).

In particular, reduced disease specific health QoL (CFQ-R) has also previously been shown to be related to impaired sleep quality even in clinically stable CF patients

(Bouka et al., 2012). Sleep disturbances in individuals with CF may be due to fragmented sleep and arousals, or other respiratory events such as cough, and can impact the subjects' perception of sleep quality and in turn poor sleep quality may impact the overall QoL (Katz, 2014, Milross et al., 2002).

Sleep disturbance can be measured subjectively by sleep specific QoL questionnaires but it can also be objectively measured using polysomnography or non-invasive methods, such as the Sonomat. The results of these objective measurements can be found in this thesis in Chapters 4 and 5. This present chapter investigates the sleep quality and overall QoL of adults with CF using both subjective measures (PSQI and ESS) as well as objective measures of sleep (using parameters of the PSG and Sonomat). The way in which the sleep quality impacts on overall QoL and impact of the CF lung disease state will be examined.

6.2 AIMS

1. To investigate sleep quality together with quality of life in adults with CF using subjective measures (PSQI, CF QoL and CFQ-R).
2. To assess the impact of lung function and subjective and objective (PSG / Sonomat) measures of sleep on overall QoL.
3. To assess the impact of worsening CF lung function on both subjective (PSQI, CF QoL and CFQ-R) and objective (PSG / Sonomat) measures of sleep quality and overall quality of life.

6.3 HYPOTHESES

1. Quality of life is related to subjective sleep quality in CF subjects.
2. Lung function and sleep parameters are correlated with quality of life in adults with CF.
3. Overall quality of life and sleep quality deteriorate as lung function deteriorates in CF subjects.

6.4 METHODS

6.4.1 Quality of Life and Sleep Quality in Adults with CF Attending a Single CF Centre.

Subjects

In a prospective, cross-sectional study, adults with CF attending the CF Clinic at Westmead Hospital were recruited. All patients were approached and offered the opportunity to complete questionnaires. Subjects were not recruited if: they did not attend an outpatient clinic appointment between 1st January 2013 and 30th November 2016; or chose not to complete the questionnaires. All subjects had a diagnosis of CF confirmed on standard clinical criteria. The protocols were all approved by the Westmead Hospital Human Research Ethics Committee (HREC2012/12/4.9(3627) AU RED HREC/12/WMEAD/427. Written informed consent was obtained for all subjects.

Baseline Characteristics

Standard anthropometric data were recorded including: weight, height, body mass index (BMI); Spirometry (forced expiratory volume in 1 second, (FEV_1) and forced vital capacity (FVC)); as well as CFTR genotype. All responses to the questionnaires were de-identified but linked to clinical data.

Questionnaires

The subjects completed three questionnaires related to sleep and overall quality of life: i) Cystic Fibrosis Questionnaire – revised (CFQ-R) (Quittner et al., 2005); ii) CF Quality of Life (CF QoL) questionnaire (Gee et al., 2000); iii) Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Details of these questionnaires can be found in Chapter 2 - Methods. The respondents also had an opportunity to speak to their specialist CF physician if questions arose following completion of the questionnaires.

The CFQ-R questionnaire is a disease-specific questionnaire that measures health related quality of life for people with CF older than 14 years over the preceding 2 weeks (Quittner et al., 2005). This questionnaire consists of 44 items on 12 generic and disease-specific scales. It encompasses general domains of quality of life: physical functioning, role functioning, vitality, health perceptions, emotional functioning and social functioning; as well as domains specific to CF: body image, eating disturbances, treatment burden, and respiratory and digestive symptoms (Quittner et al., 2005). Each item included ratings of frequency or difficulty on a 4-point scale (where 1 = always, 2 = often, 3 = sometimes, 4 = never; or 1 = very true, 2 = somewhat true, 3 = somewhat

false, 4 = very false; see Table 2.2). Scores are then standardised on a 0 to 100-point scale, with higher scores representing better quality of life for each particular domain.

The CF Quality of Life questionnaire (CF QoL) measures the self-described quality of life over the previous 2 weeks in several domains (Gee et al., 2000). This questionnaire contains 52 items in total which covers the 8 domains of: physical functioning; social functioning; treatment issues and chest symptoms; emotional functioning; concerns for the future; interpersonal relationships; body image; and career concerns. All items are scored from 1 to 6 and then scaled to produce a transformed score of between 0 and 100 for each section. A transformed score indicates the value that has been achieved out of a maximum of 100 with 100 indicating the most positive QoL levels possible. The total QoL score is scored out of 312 (52 questions, each with a score up to 6).

The PSQI consists of 19 questions with seven domains of sleep covered including: duration of sleep; sleep disturbance; sleep latency; daytime dysfunction due to sleepiness; sleep efficiency; overall subjective sleep quality; requirement of medications to sleep. The range of values for each scored domain is 0 to 3 points. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven domain scores are then added to yield one "global" score, with a range of 0 to 21 points, "0" indicating no difficulty and "21" indicating severe difficulties in all areas. A global PSQI score of greater than 5 indicates that a subject is a "poor sleeper" (Buysse et al., 1989).

6.4.2 Subjective and Objective Sleep Quality and QoL Data for the Adults with CF undergoing PSG and Sonomat Studies.

Subjects

Subjects (n = 40) who underwent an overnight diagnostic sleep study (in Chapter 4) also completed the sleep specific questionnaires: Epworth Sleepiness Scale (ESS) (Johns, 1991) and PQSI; as well as the disease-specific questionnaires: CFQ-R and CF QoL, on the night of the study and the results of these studies are presented below. These subjects also performed spirometry as part of the baseline demographic data collection.

Epworth Sleepiness Scale

As described in Chapter 2 – Methods, the Epworth Sleepiness Scale is a measurement of daytime sleepiness (Johns, 1991). It is a self-administered questionnaire and the subjects were asked to rate on a scale of 0 to 3 the likelihood of dozing off in eight different situations (Johns, 1991). The raw numbers were then added to give a score between 0 and 24. A raw score of 10 or greater in the general population suggests increased daytime somnolence (Johns, 1991).

Polysomnography

In addition to the above questionnaire data collected for all participants, data from the polysomnogram (reported in Chapter 4) were recorded to assess objective measures of sleep disturbance and compare these results with results of QoL questionnaires.

Data from the polysomnogram performed in 40 subjects reported in Chapter 4 – Table 4.2 included: Sleep efficiency (SE); Arousal index (AI); Respiratory disturbance index (RDI); Apnoea-hypopnoea index (AHI); total sleep time; REM sleep %; NREM sleep %; Wakefulness after sleep onset (WASO). Oximetry data included: Baseline SpO_2; mean SpO_2 during sleep; oxygen desaturation index (ODI); nadir SpO_2. In addition, respiratory, leg and spontaneous arousals were also documented in Table 4.3 – Sleep Arousal Results.

Furthermore, to look at comparisons with previous studies (Young et al., 2011), desaturators with a 10 % threshold were defined as subjects spending ≥ 10 % of recording time with SpO_2 < 90 %. Desaturators with a 30 % threshold were defined as subjects spending ≥ 30 % of recording time with SpO_2 < 90 %.

Sonomat

The Sonomat was used to calculate the % of total sleep time in which coughs and crackles present were present during the night. Description of the classification of adventitial sounds was described in Chapter 4 – Cross Sectional Objective Sleep Measurements in Adults with CF.

Lung Function

Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society criteria (Miller et al., 2005). Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were recorded. Predicted spirometric parameters were derived using reference values from Hankinson et al, 1999 (Hankinson et al., 1999).

6.4.3 Sleep Quality and QoL in a Subset of Adults with CF with Deteriorating Lung Function.

Subjects

Eight patients were enrolled who had clinical deterioration over a 1 to 3 year period with: reductions in lung function (between 2 and 24 % drop in FEV_1 % predicted); frequent exacerbations (> 4 in the preceding 12 months); or worsening daytime hypoxaemia.

Measurements

Overnight polysomnography along with the Sonomat, questionnaires (CFQ-R, CFQoL, PSQI and ESS) and lung function were repeated 1 to 3 years following their first study, again at the end of an admission for an exacerbation. These above measures have been described in detail in Chapter 2 – Methods.

6.4.4 Statistical Analyses

Statistical and graphical analyses were performed using SPPS version 22 (SPSS Inc., IL, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). Normally distributed data were presented as mean ± standard deviation (SD), and non-normally distributed data were presented as median and interquartile range (IQR). Correlation was performed using Spearman's correlation analyses. Results were deemed statistically significant if $p < 0.05$. For correlation data, regression lines were shown on the graphs with r^2, r and p-values reported.

6.5 RESULTS

6.5.1 Quality of Life and Sleep Quality in Adults with CF Attending a Single CF Centre.

One hundred and twenty participants completed the 3 questionnaires at the time of their routine CF clinic visit. This represented an overall response rate of 74 % (120 / 162) of the total patient clinic population at that time. Detailed baseline characteristics of the group are shown in Table 6.1 below. The mean FEV_1 was 64 % predicted which demonstrated an overall moderate disease category with a large range from 17 % (very severe) to 117 % (normal) FEV_1 % predicted. The mean BMI was in the normal weight category at 22.1 kg/m^2. As expected, approximately half of the participants were homozygous for F508 del (47 %).

Table 6.1 Baseline Characteristics for QoL Data

Characteristic	**Results**
Male (n, %)	58, 48
Age, years (mean ± SD)	29.0 ± 9.6
F508del homozygous (n, %)	56, 47
BMI, kg/m^2 (mean ± SD)	22.4 ± 3.3
FEV_1, % predicted (mean ± SD)	65.6 ± 23.3 (range 17-117 %)

N = 120 subjects. Data presented as mean ± SD. BMI: body mass index. FEV_1: forced expiratory volume in 1 second.

Results for each of the domains of the 3 questionnaires are detailed in the following Tables (Tables 6.2 to 6.5). The transformed scores for CFQ-R, CF QoL and PSQI demonstrated the variation in different domains of QoL for these CF subjects.

CFQ-R Results

Table 6.2 CFQ-R Results

CFQ-R Domain	
Physical functioning	75.0 (45.8)
Vitality	54.0 ± 20.7
Emotion	80.0 (33.3)
Eating	100.0 (22.2)
Treatment Burden	50.8 ± 22.5
Health Perceptions	58.9 ± 24.5
Social	66.2 ± 19.2
Body Image	77.8 (55.6)
Role	83.3 (25.0)
Weight	66.7 (66.7)
Respiratory	66.7, 33.3
Digestive System	88.9 (22.2)

N = 120 subjects. CFQ-R: CF Questionnaire - Revised. Transformed scores: 0 = worst, 100 = best QoL possible. Normally distributed data expressed as mean ± SD. Non-normally distributed data expressed as median (IQR).

Of the scores which demonstrated the highest level of quality of life, the "eating" domain scored the highest with a median score of 100 (IQR of 22.2). There was a discrepancy, however, with "weight" and "body image" domains which scored lower with medians at 66.7 and 77.8, respectively, compared with those scored for "eating". In keeping with their disease severity as a group, the participants reported "respiratory

symptoms" as lower with a median of 66.7 (IQR 33). Our group also perceived their health as between "fair" and "good" with a median of 66.7 (IQR 33). Despite their reporting of reduced health, the CF participants reported higher quality of life in terms of the "role" domain which focuses on their ability to keep up with daily activities.

As detailed in Table 6.2, body image had a median transformed score of 77.8 out of a possible score of 100 indicating that in our patients, body image was perceived as positive rather than negative. In addition, looking at gender and body image, we found that the median transformed score for males was 66.7 (IQR 44.4) and for females it was 77.8 (IQR 44.4) suggesting that females have better body image perception than males, and this was found to be statistically significant ($p = 0.039$).

CF QoL Results

Table 6.3 CF QoL Questionnaire Results

QoL Domain	Results
Physical functioning	91.0 (26.0)
Social functioning	90.0 (23.8)
Treatment issues	66.7 (40.0)
Chest symptoms	80.0 (30.0)
Emotional functioning	87.5 (25.0)
Future concerns	45.6 ± 24.3
Relationships	62.0 (41.5)
Body image	73.3 (40.0)
Career concerns	70.0 (45.0)
Total CF QoL	236.5 (66.8)

N = 120 subjects. Units: arbitrary units. Data expressed as mean ± SD for normally distributed data and median (inter-quartile range) for non-normally distributed data. Transformed scores: 0 = worst, 100 = most positive QoL levels possible. Total CF QoL scored out of possible 312 points.

Looking at each domain separately, the areas where patients indicated poorest quality of life included: treatment issues, future concerns, relationships and career concerns.

PSQI Results

The results of the sleep specific questionnaire, the PSQI, are shown below in Table 6.4. For each domain, there was a total score out of 3, with the combined score out of a total of 21. A global PSQI score of greater than 5 indicated poorer subjective sleep quality (Figure 6.1), with 52 subjects (43 %) scoring above 5.

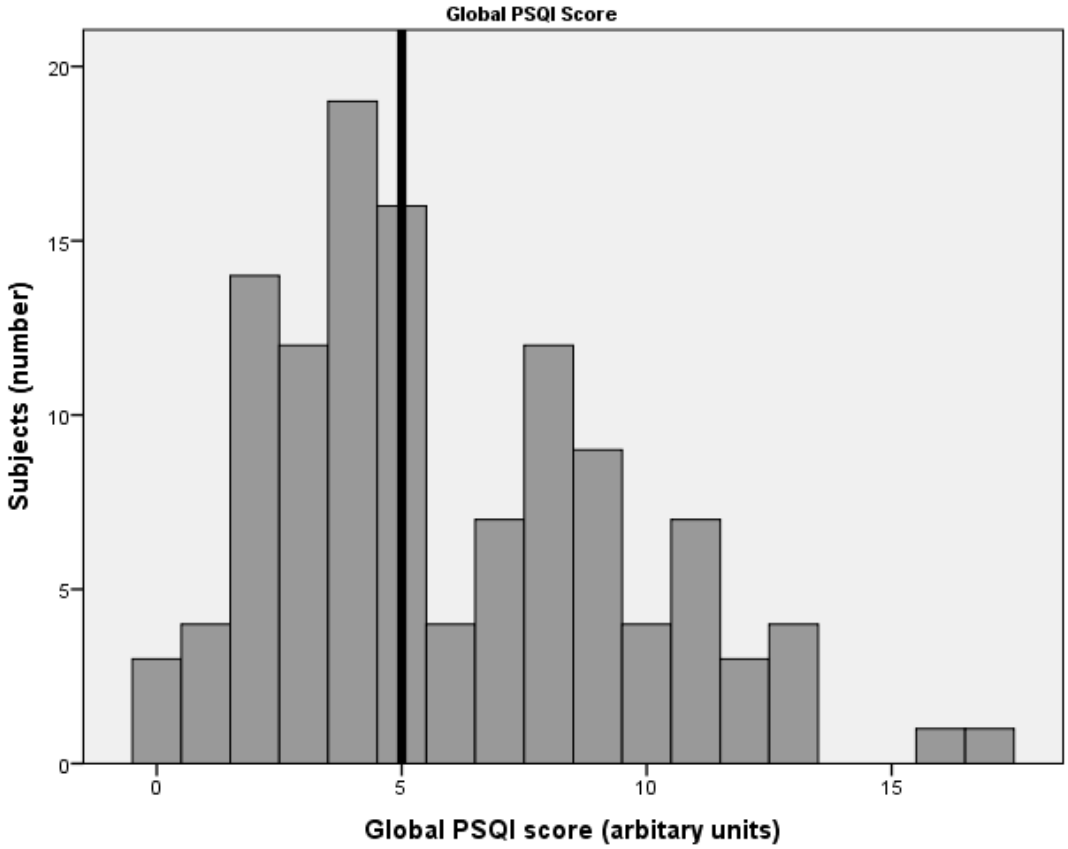

Figure 6.1 Global PSQI score

PSQI: Pittsburgh Sleep Quality Index. Units are arbitrary units. Global score out of 21. A global score greater than 5 indicated poorer sleep quality.

Table 6.4 PSQI results

PSQI Domain	Results
Sleep Duration	0.4 ± 0.8
Sleep Disturbance	1.4 ± 0.6
Sleep Latency	1.2 ± 1.1
Daytime Dysfunction	1.0 ± 0.9
Sleep Efficiency	0.7 ± 1.0
Sleep Quality	1.1 ± 0.8
Sleep Medications	0.1 ± 0.5
Global PSQI score	5.9 ± 3.6

N = 120 subjects. Data expressed as mean ± SD. Units are arbitrary units. PSQI: Pittsburgh Sleep Quality Index. Each domain is scored out of 3, (0 = best, 3 = worst), with total global score out of 21.

The above results for PSQI indicated that in our adult CF population, there was increased reporting of poor subjective sleep quality with a mean PSQI score of 5.9 (SD ± 3.6). Range of total scores from 1 to 17 (total out of 21). Out of a total of 3 for each separate question, the domain of sleep disturbance represented the highest score with a mean at 1.4 units.

Lung Function

CFQ-R and Lung Function

Using Spearman's test of correlation, significant correlation was found between FEV_1 for the domains of: physical functioning, eating, treatment burden, health perceptions, social role, body image, role, weight and respiratory issues (Table 6.5).

Table 6.5 CFQ-R Domains and Correlation with FEV_1

CFQ-R domain	Correlation with FEV_1		
	p-value	**r**	**r^2**
Physical functioning	0.001	0.551	0.305
Vitality	0.022	0.210	0.039
Emotion	0.176 NS	0.124	0.010
Eating	0.005	0.255	0.068
Treatment Burden	0.001	0.295	0.089
Health Perceptions	0.001	0.475	0.247
Social	0.004	0.260	0.065
Body Image	0.001	0.310	0.117
Role	0.001	0.350	0.133
Weight Issues	0.002	0.282	0.100
Respiratory Issues	0.001	0.299	0.070
Digestion Issues	0.788 NS	0.025	0.042

N = 120 subjects. CFQ-R: CF questionnaire – revised; FEV_1: forced expiratory volume in 1 second; NS: not significant. Using Spearman's rho, where correlation is significant at the 0.05 level (2-tailed).

Two domains were not correlated with FEV_1: emotion and digestion with p-value not significant, as shown in Table 6.5. Below are graphs representing select CFQ-R domains – physical and heath perception domains, presenting the correlations with lung function (FEV_1 % predicted), Figures 6.2 and 6.3.

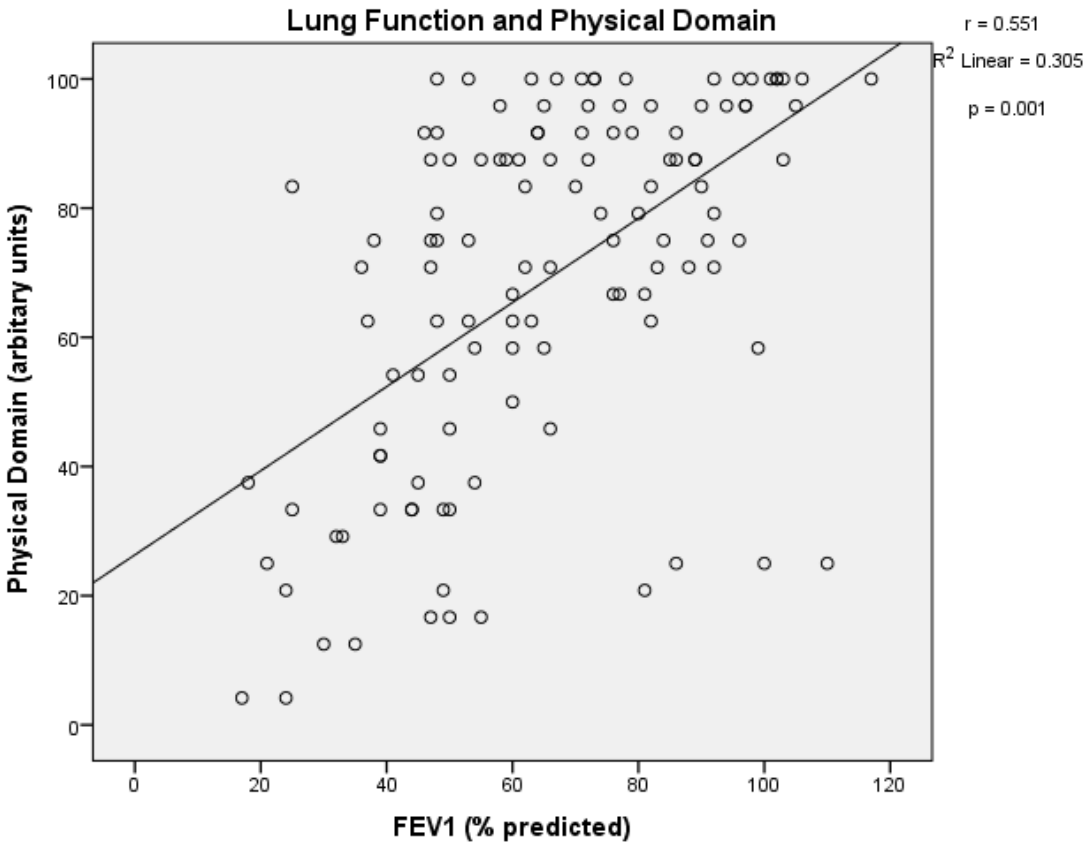

Figure 6.2 Lung Function and Physical Domain

FEV_1: Forced expiratory volume in 1 second.

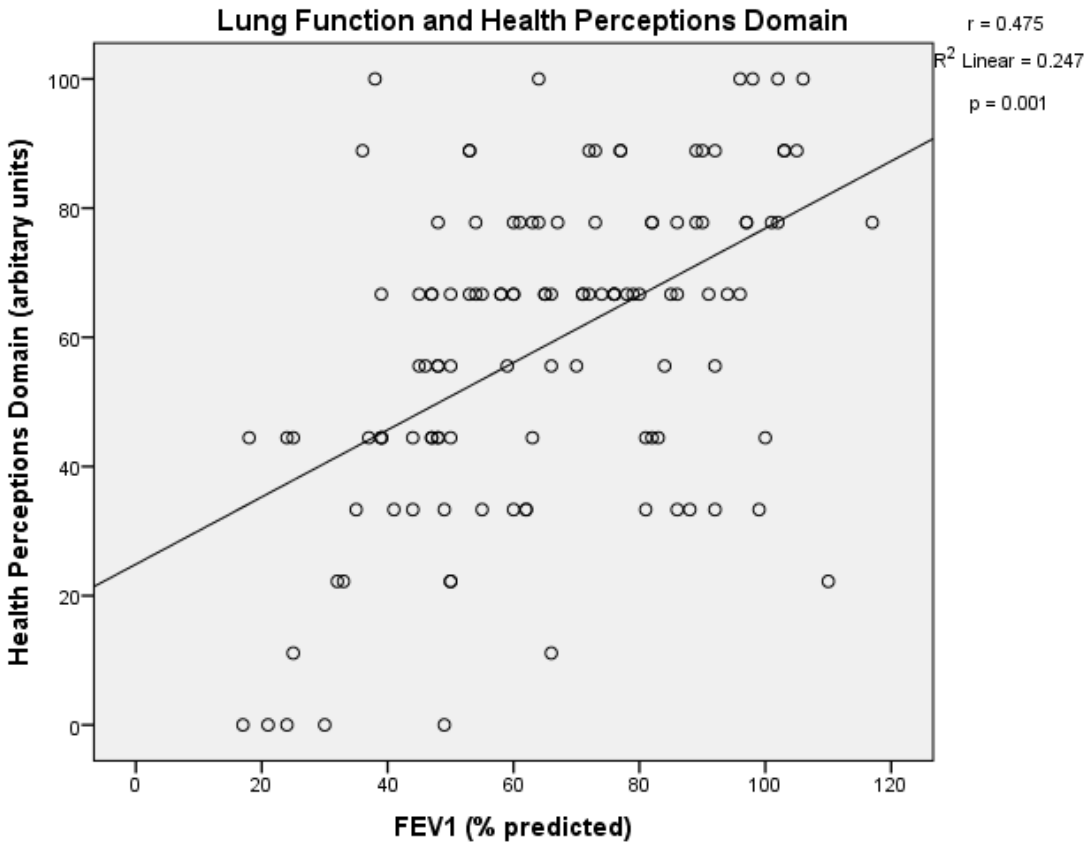

Figure 6.3 Lung Function and Health Perceptions Domain

FEV_1: Forced expiratory volume in 1 second.

CF QoL and Lung Function

Using Spearman's calculation for correlation, total CF QoL score was statistically significantly correlated (p = 0.001) with FEV_1 (r = 0.345; r^2 = 0.130), see Figure 6.4, although there was a wide variation in QoL for different adults with similar FEV_1. There was no correlation between total CF QoL score and either BMI or gender (p = 0.704 and 0.483, respectively).

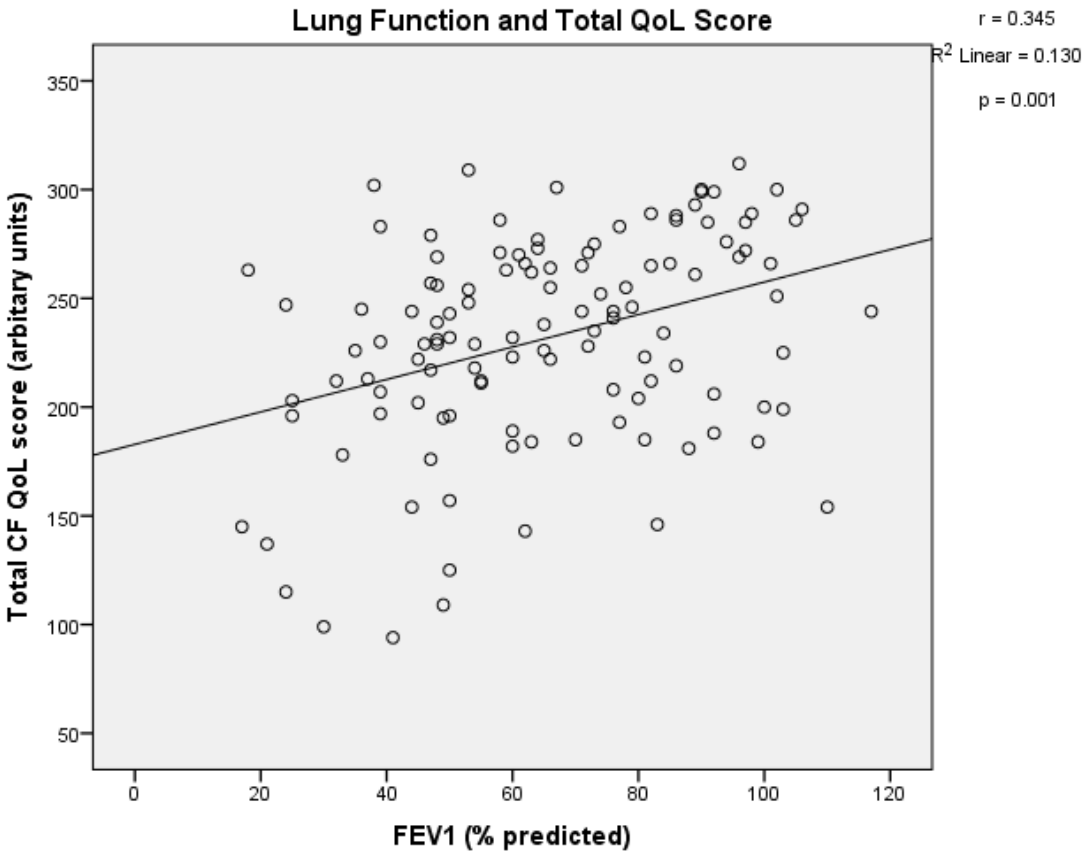

Figure 6.4 Lung Function and Total CF QoL Score.

CF QoL: Cystic Fibrosis Quality of Life Questionnaire. FEV_1: Forced expiratory volume in 1 second. Line on graph is regression line.

All domains of the CF QoL except emotional functioning and concerns for the future correlated significantly with FEV_1 (Table 6.6), using Spearman's correlation test.

Table 6.6 CF QoL Domains and Correlation with FEV_1

CF QoL Domain	Correlation with Lung Function		
	p-value	r	r^2
Physical functioning	0.001	0.490	0.231
Social functioning	0.005	0.257	0.084
Treatment issues	0.001	0.310	0.095
Chest symptoms	0.001	0.315	0.101
Emotional functioning	0.057 NS	0.174	0.010
Future concerns	0.157 NS	0.130	0.013
Relationships	0.001	0.293	0.086
Body image	0.002	0.276	0.085
Career concerns	0.002	0.284	0.074
Total CF QoL	0.001	0.345	0.130

N = 120 subjects. FEV_1: forced expiratory volume in 1 second; QoL: Quality of Life; NS: not significant. Correlation was significant at the 0.05 level (2-tailed) using Spearman's correlation test.

PSQI and Lung Function

Importantly, total global PSQI was only weakly correlated with FEV_1 ($r = -0.292$; $p = 0.001$; $r^2 = 0.085$), shown in Figure 6.5 below. Of the adults with a FEV_1 % predicted < 35 % (n = 9) only 1 reported a normal PSQI score of < 5 arbitrary units.

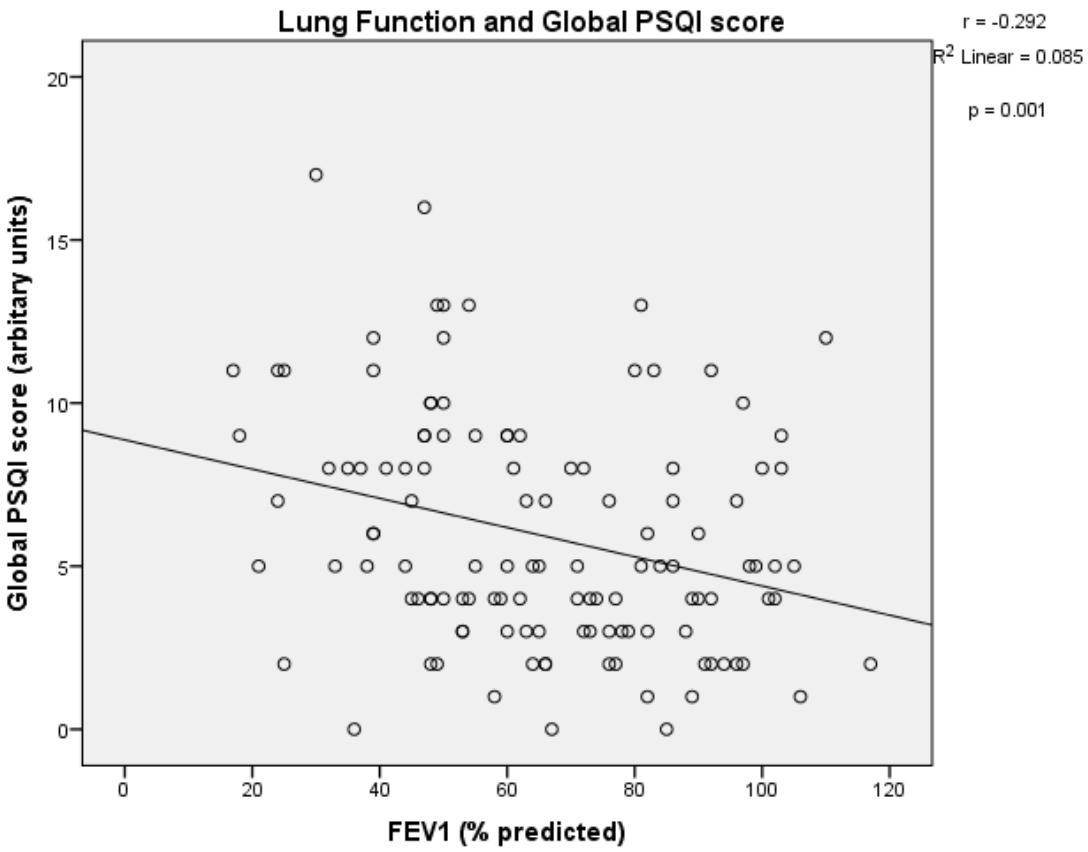

Figure 6.5 Lung Function and Global PSQI score

PSQI: Pittsburgh Sleep Quality Index; FEV_1: Forced expiratory volume in 1 second.

We also looked at the correlation between overall QoL using the CF QoL questionnaire and the sleep specific questionnaire, the PSQI, and found they were strongly negatively correlated ($r = -0.508$; $p = 0.001$; $r^2 = 0.286$) (Figure 6.6). Those subjects with higher overall CF QoL scores also scored lower on the PSQI.

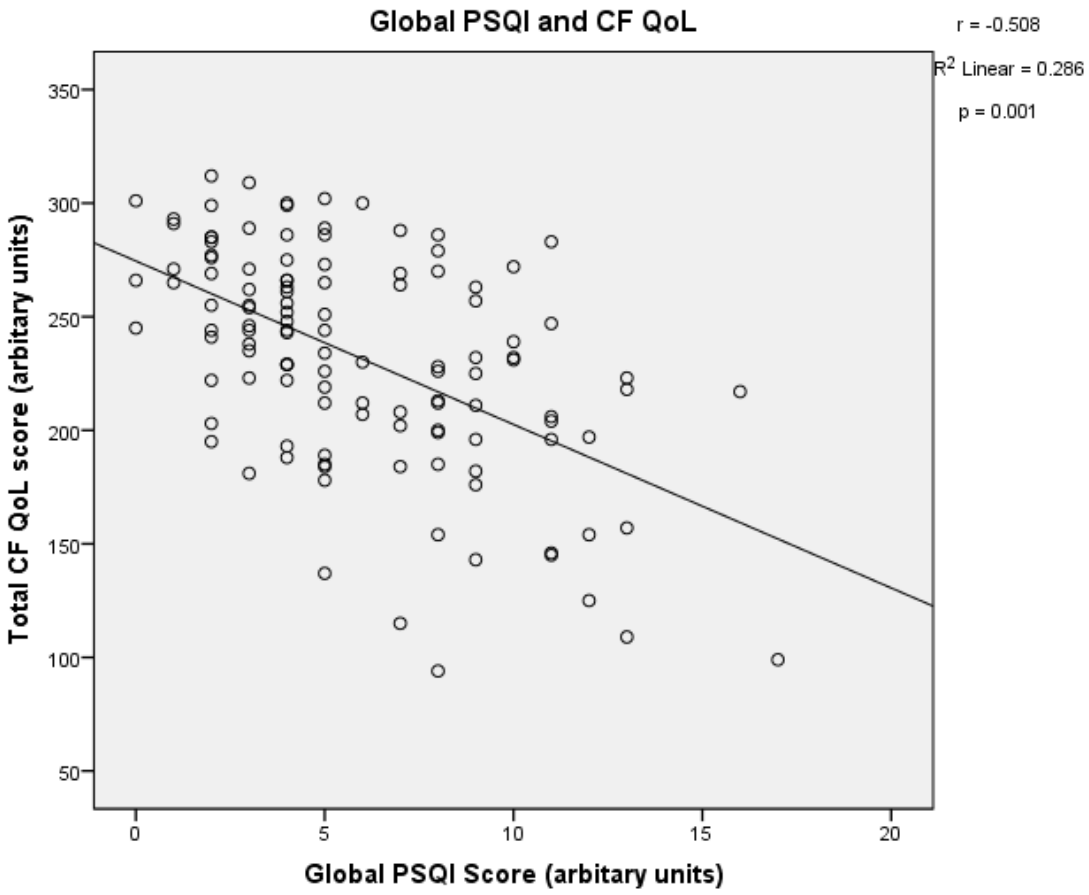

Figure 6.6 PSQI and CF QoL scores

PSQI: Pittsburgh Sleep Quality Index; QoL: Quality of Life.

6.5.2 Subjective and Objective Sleep Quality and QoL Data for the Adults with CF undergoing PSG and Sonomat Studies.

The baseline characteristics of subjects who participated in this study has been shown in Table 4.1 in Chapter 4. Of the 40 subjects, 16 were male and the mean age of all participants was 33.8 years (SD ± 10.8). In this smaller study, the average FEV_1 % predicted was in the severe range at 47.9 %.

Subjective Measures

Table 6.7 Subjective Sleep Quality

Subjective Measures	**Results**
Total CF QoL, arbitrary units	206.9 ± 50.6
PSQI, arbitrary units	7.3 ± 3.3
ESS, arbitrary units	5.4 ± 3.0

N = 40 subjects. Data expressed as mean ± SD. CF QoL: Cystic Fibrosis Quality of Life Questionnaire; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale.

Table 6.8 Subjective Sleep Quality and Lung Function

Subjective Sleep Quality Variables	**Correlation with lung function (FEV_1)**		
	p-value	**r**	**r^2**
Total CF QoL	0.073	0.286	0.100
PSQI	0.394	-0.139	0.028
ESS	0.817	-0.038	0.001

N = 40 subjects. FEV_1: forced expiratory volume in 1 second; CF QoL: Cystic Fibrosis Quality of Life Questionnaire; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale.

As shown in Table 6.8, there were no statistically significant correlations between subjective sleep quality and lung function.

Table 6.9 Subjective QoL Results in Desaturators vs Non-desaturators

Characteristic	Non-desaturators (n = 28)	Desaturators (n = 12)	p-value
Age, years	32.3 ± 9.5	36.5 ± 13.2	NS
Gender	F 20, M 8	F 4, M 8	NS
BMI, kg/m^2	21.6 ± 3.3	21.4 ± 3.1	NS
FEV_1, % predicted	53.9 ± 16.6	33.8 ± 11.7	0.001
Baseline SpO_2, %	95.9 ± 1.5	93.2 ± 2.8	0.001
Total CF QoL (total out of 312)	212.4 ± 44.7	194.0 ± 62.8	NS
PSQI (0 = best, 21 = worst)	7.1 ± 3.0	7.6 ± 4.3	NS
ESS (0 = best, 24 = worst)	4.9 ± 2.3	6.5 ± 4.3	NS

N = 40 subjects. Data expressed as mean ± SD. NS: not significant; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; SpO_2: oxygen saturation; CF QoL: Cystic Fibrosis Quality of Life Questionnaire; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; Desaturators: Desaturators are classified as those subjects who spent ≥ 10 % of recording time with SpO_2 < 90 % (n = 12 subjects); Non-desaturators (n = 28 subjects).

When dividing the group into desaturators (oxygen saturation of < 90 % for more than 10 % of total recording time) and non-desaturators, as expected, the FEV_1 was significantly different with a mean of 33.8 % predicted for the desaturators, and 53.9 FEV_1 % predicted for the non-desaturators (p = 0.001). In addition, awake SpO_2 differed for the two groups, where desaturators had an awake SpO_2 of 93.2 % compared with 95.9 % for the non-desaturators group (p = 0.001). When looking at each of the

domains of the CFQ-R, quality of life appeared unrelated to more severe nocturnal hypoxaemia (all p-values were not significant).

Objective Measures

Polysomnography

Polysomnography data have been previously described in detail in Table 4.2, Chapter 4. In addition, types of arousals and details of desaturators and non-desaturators can be found below in Table 6.10.

Table 6.10 Polysomnogram Results

PSG Sleep Characteristic	**Results**
Respiratory arousals, events per hour	4.5 (8.5)
Leg arousals, events per hour	0.0 (0.2)
Spontaneous arousals, events per hour	8.2 (9.1)
Desaturators 10% threshold, n (%)	12 (30 %)
Desaturators 30% threshold, n (%)	7 (17.5 %)

N = 40 subjects. Data expressed as median (IQR). PSG: polysomnogram; Desaturators 10 % threshold = Subjects spending ≥ 10 % of recording time with SpO_2 < 90 %; Desaturators 30 % threshold = Subjects spending ≥ 30 % of recording time with SpO_2 < 90 %.

Lung function and objective sleep quality based on the PSG did not appear to be related, except for those oximetry parameters including awake SpO_2, nadir SpO_2 and time spent

with SpO_2 < 90 % shown previously in Table 4.6 in Chapter 4. Using linear regression to assess influence of lung function (FEV_1 % predicted) on sleep parameters, only awake SpO_2 and nadir SpO_2 were positively correlated weakly with FEV_1 % predicted ($p = 0.001$ and $p = 0.003$; $r^2 = 0.253$ and 0.186; respectively).

Sonomat

The Sonomat showed no significant correlations between Sonomat parameters (cough and crackles during sleep) and any of the sleep quality and QoL questionnaires, as shown in Tables 6.11 – 6.13 below.

Table 6.11 Sonomat Variables and ESS

Sonomat Sleep Quality Variables	**Correlation with ESS**		
	p-value	**r**	**r^2**
Crackles, % of total sleep time	0.604	-0.084	0.004
Cough, % of total sleep time	0.204	0.205	0.001

N = 40 subjects. ESS: Epworth Sleepiness Scale

Table 6.12 Sonomat Variables and PSQI

Sonomat Sleep Quality Variables	**Correlation with PSQI**		
	p-value	**r**	**r^2**
Crackles, % of total sleep time	0.449	0.125	0.0009
Cough, % of total sleep time	0.936	0.013	0.002

N = 40 subjects. PSQI: Pittsburgh Sleep Quality Index.

Table 6.13 Sonomat Variables and Total CF QoL Score

Sonomat Sleep Quality Variables	Correlation with Total CF QoL score		
	p-value	r	r^2
Crackles, % of total sleep time	0.698	-0.063	0.0002
Cough, % of total sleep time	0.056	-0.305	0.150

N = 40 subjects. CF QoL: Cystic Fibrosis Quality of Life questionnaire.

6.5.3 Sleep Quality and QoL in a Subset of Adults with CF with Deteriorating Lung Function.

In this study, 8 subjects who had clinical deterioration over 1 - 3 years underwent objective and subjective measures of sleep quality and QoL. The demographic data of these subjects has been described previously in Table 5.1 – Patient Characteristics in Longitudinal Study in Chapter 5.

Table 6.14 Baseline and Subsequent QoL, Sleep Quality and Objective Sleep Quality Measures in Longitudinal Study.

Characteristic	Baseline	Subsequent	p-value
Total CF QoL	221.3 ± 51.5	198.0 ± 58.2	0.106
PSQI	6.8 ± 2.3	7.9 ± 3.1	0.425
ESS	3.9 ± 2.2	5.0 ± 1.8	0.122

N = 8 subjects. Data expressed as mean ± SD. CF QoL: Cystic Fibrosis Quality of Life questionnaire; PSQI; Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; * p-value significant at < 0.05.

As shown in the above table, the Total CF QoL score tended to decrease over time and the results of the ESS and PSQI tended to increase, but, none of the measures exhibited a statistically significant change over time. There was a negative correlation between total CF QoL score and PSQI with lung function at baseline but they were not statistically significant, Table 6.15.

Table 6.15 Correlation of Lung Function with QoL and Subjective Sleep Quality Parameters at Baseline

Measure	Correlation with Lung Function (FEV_1 % predicted)		
	p-value	r	r^2
Total CF QoL	0.866	-0.072	0.011
PSQI	0.753	-0.133	0.231
ESS	0.699	0.164	0.012

N = 8 subjects. FEV_1: forced expiratory volume in 1 second; CF QoL: CF quality of life questionnaire; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale. * Correlation significant at 0.05 level (2-tailed).

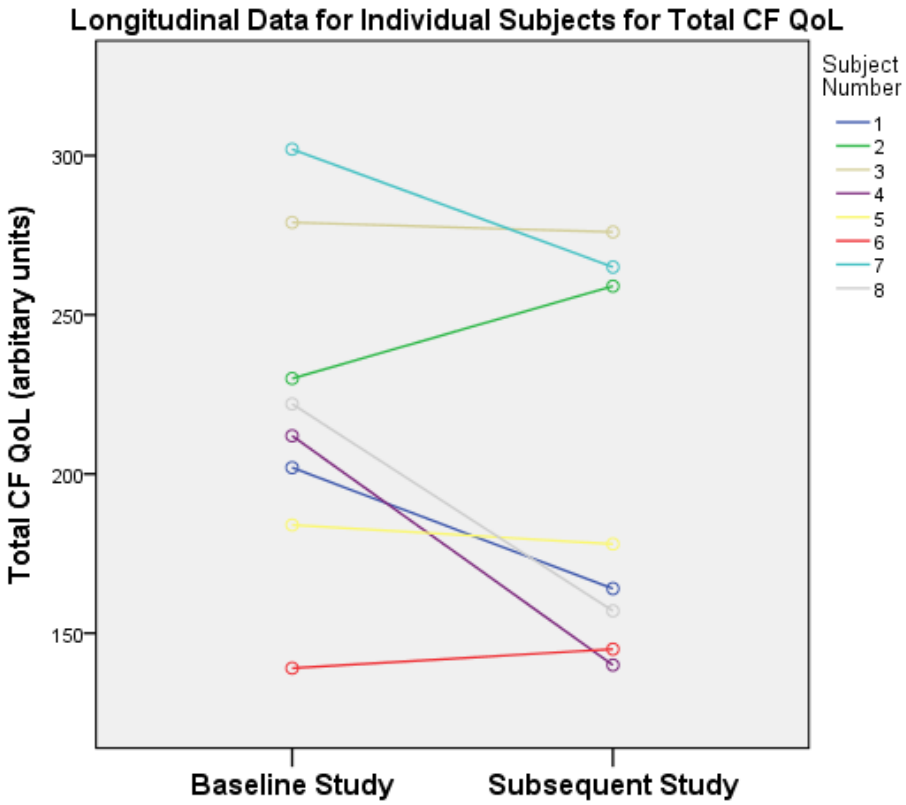

Figure 6.7 Total CF QoL at Baseline and at Subsequent Study.

CF QoL: Cystic Fibrosis Quality of Life questionnaire.

Half of the subjects reported reduction in CF QoL between baseline and subsequent studies. There were 2 subjects (subjects 2 and 6) who reported a minor increase in CF QoL scores.

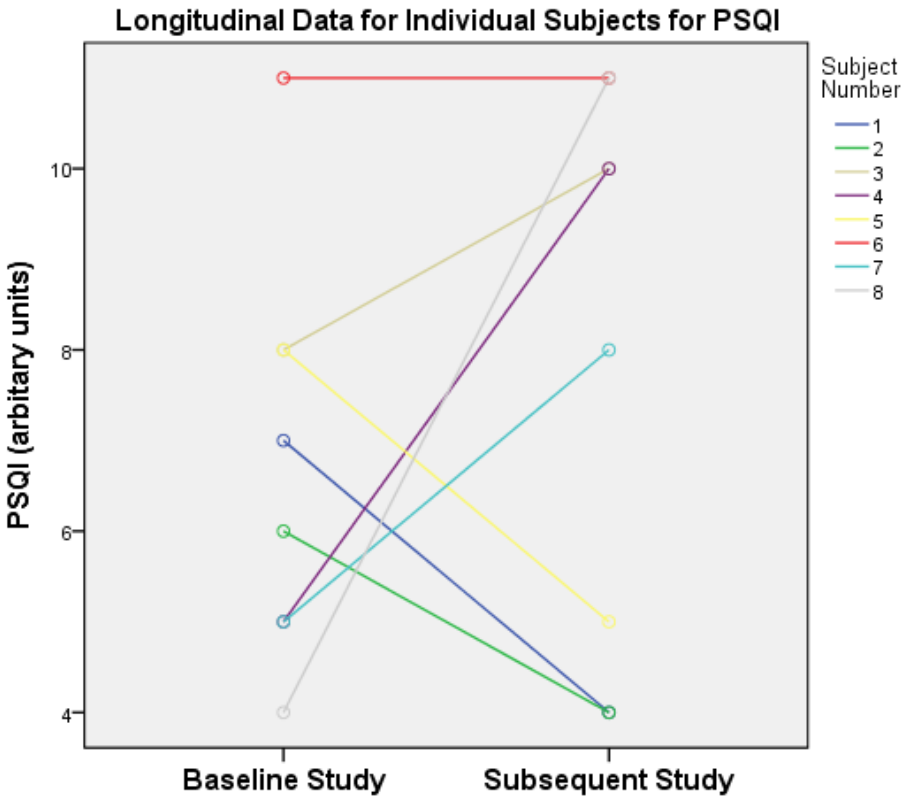

Figure 6.8 PSQI at Baseline and at Subsequent Study.

As shown in Figure 6.8, there was a wide variation in responses to PSQI between baseline and subsequent studies with half reporting worsening sleep quality, 3 reporting a mild improvement and one that did not change between the studies. The PSQI results seem unrelated to progression of disease.

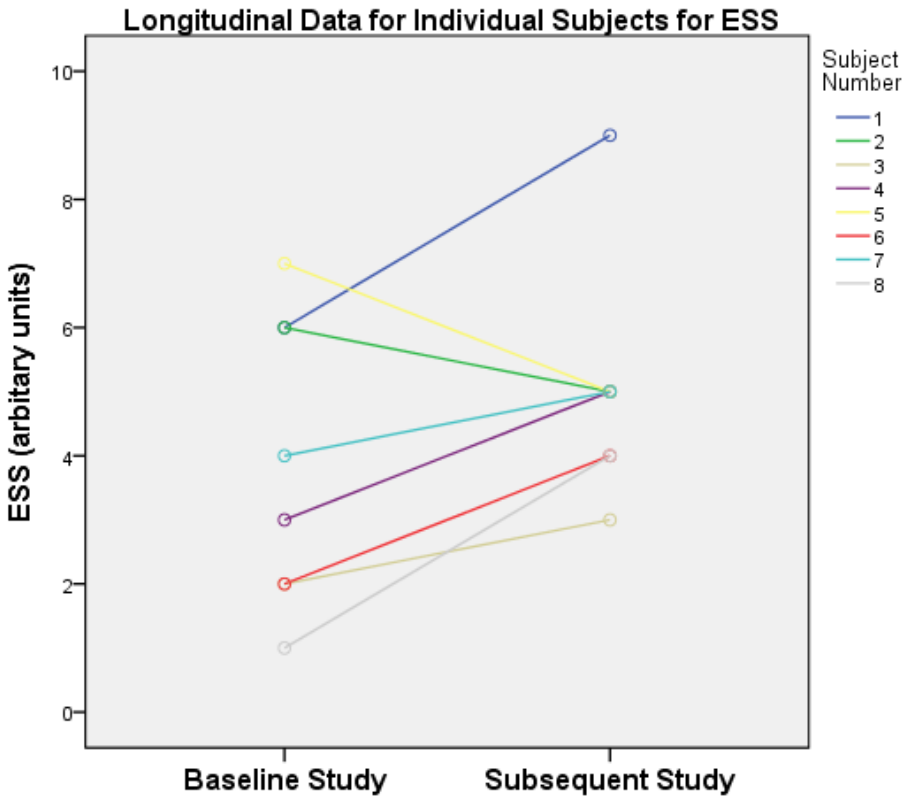

Figure 6.9 ESS at Baseline and at Subsequent Study.

ESS: Epworth Sleepiness Scale.

For ESS over time, 6 out of 8 subjects reports an increase in daytime somnolence as indicated by the increase in ESS scores, as shown in Figure 6.9.

The correlations between the change in objective sleep variables and their correlation with change in subjective QoL measures were evaluated. Using Spearman's test for correlation, none of the objective parameters of sleep from the PSG between baseline and subsequent studies were shown to be correlated with change in total CF QoL score nor change in PSQI, Table 6.16. For the change in ESS, only the change in arousal index was found to be significantly positively correlated ($p = 0.026$, $r = 0.768$, $r^2 = 0.437$), Figure 6.10.

Table 6.16 Change in Objective Sleep Measures from PSG and Correlation with Change in Subjective QoL Measures.

		Δ Total CF QoL	Δ PSQI	Δ ESS
Δ AI	p-value r r^2	0.136 -0.575 0.365	0.700 0.163 0.013	0.026* 0.768 0.437
Δ AHI	p-value r r^2	0.531 -0.262 0.035	0.866 0.072 0.005	0.932 0.036 0.0001
Δ RDI	p-value r r^2	0.320 -0.405 0.075	0.756 -0.132 0.023	0.775 0.121 0.005
Δ Awake SpO_2	p-value r r^2	0.865 -0.072 0.0008	0.853 -0.079 0.007	0.943 -0.031 0.061
Δ Nadir SpO_2	p-value r r^2	0.799 0.108 0.0008	0.606 -0.217 0.0006	0.643 0.195 0.025

Subjects: n = 8. QoL: Quality of Life; AI: arousal index; AHI: apnoea-hypopnoea index; RDI: respiratory disturbance index; SpO_2: oxygen saturation; CF QoL: Cystic Fibrosis Quality of Life questionnaire; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale. * significance at $p < 0.05$.

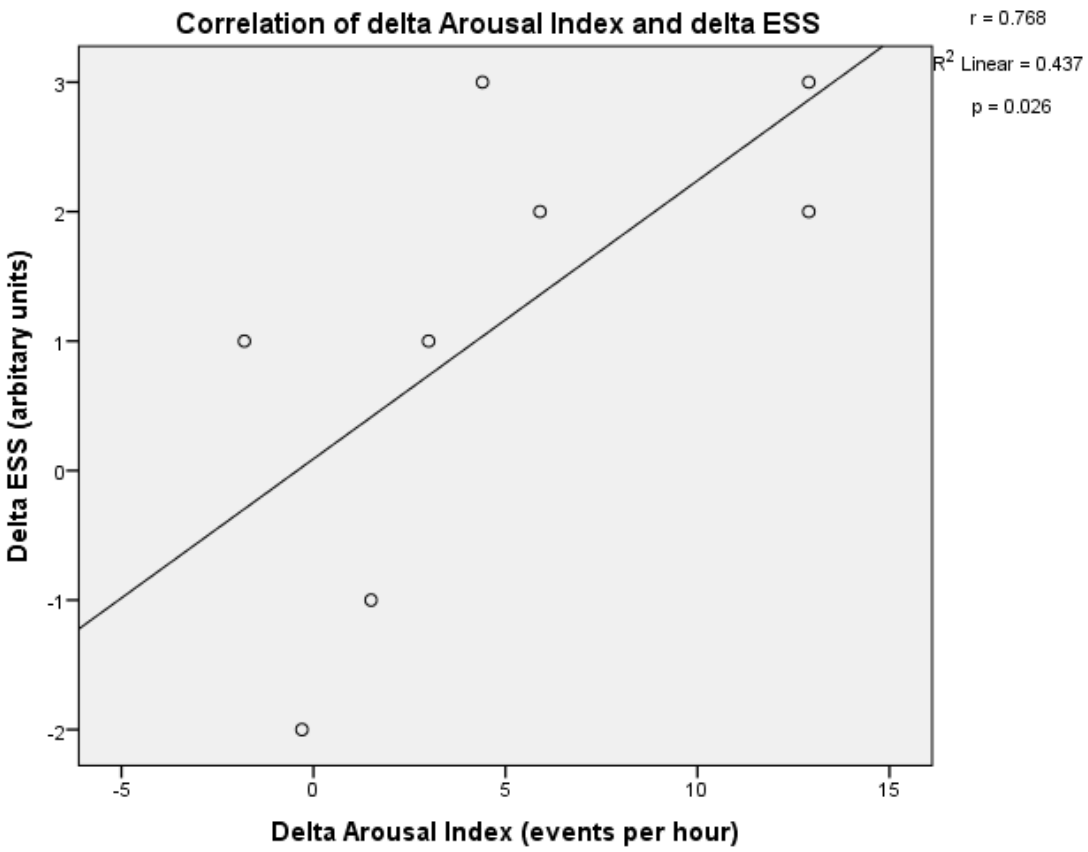

Figure 6.10 Correlation of Change in AI and Change in ESS.

AI: Arousal Index; ESS: Epworth Sleepiness Scale.

Although, there were no statistically significant correlations between change in lung function (FEV_1 % predicted) and change in subjective sleep quality and QoL measures (CF QoL, PSQI and ESS), there was a trend towards a correlation between change in lung function and change in CF QoL ($p = 0.071$, $r = 0.667$, $r^2 = 0.320$), shown in Figure 6.11.

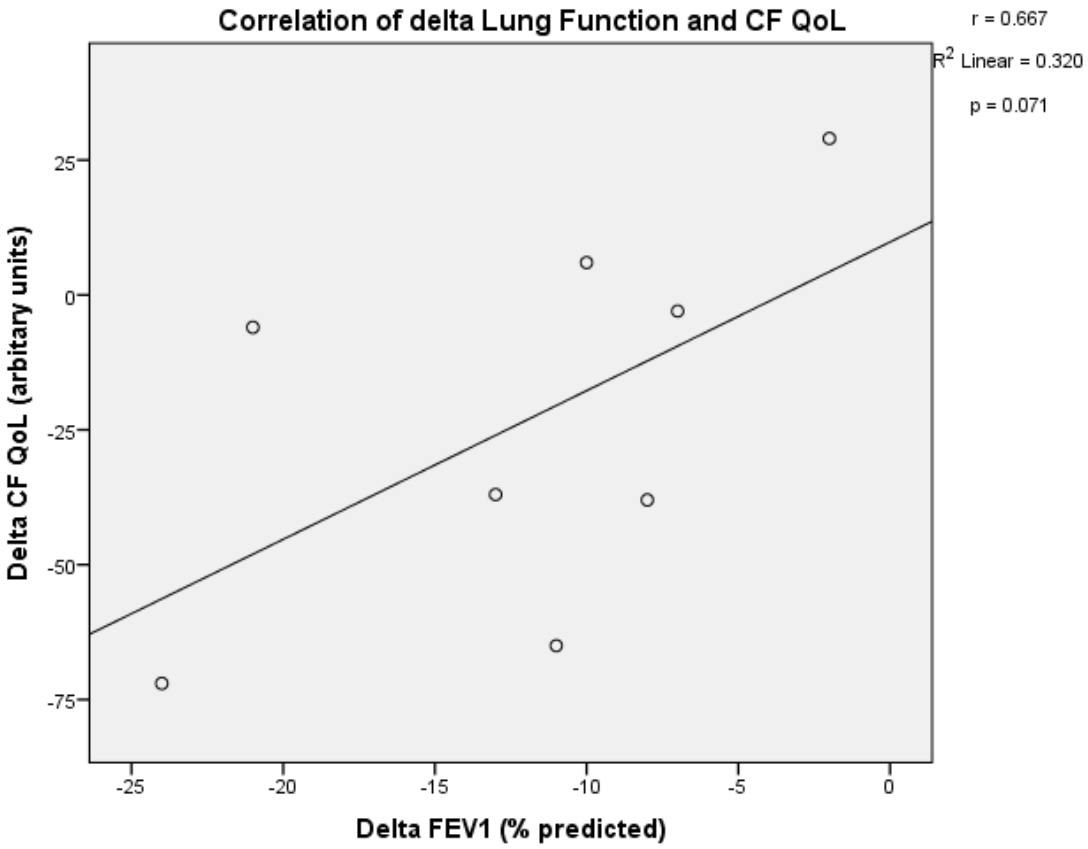

Figure 6.11 Correlation of Change in Lung Function and Change in CF QoL

FEV_1: Forced expiratory volume in 1 second; CF QoL: Cystic Fibrosis Quality of Life questionnaire.

There were no correlations identified between change on CF QoL or change in PSQI nor change in ESS, Table 6.17.

Table 6.17 Correlations between Changes in QoL Measures over Time.

Measure	Correlation with Δ Total CF QoL		
	p-value	r	r^2
Δ **PSQI**	0.204	-0.503	0.483
Δ **ESS**	0.120	-0.594	0.413

CF QoL: Cystic Fibrosis Quality of Life questionnaire; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale.

6.6 DISCUSSION

6.6.1 Quality of Life and Sleep Quality in Adults with CF Attending a Single CF Centre.

Comparing the results of the CFQ-R in our study with those reported in the large landmark study by Quittner et al. (2012), many of the findings (except treatment burden and health perceptions) were similar (Quittner et al., 2012). In their study, the FEV_1 % predicted and BMI were similar to ours (FEV_1 % predicted: 66.5 ± 25.1 % and BMI: 21.1 ± 3.3 kg/m^2) (mean ± SD) in their teen/adult subset. Hence, their patient population as based on lung disease severity and BMI in the US, was similar to our population in Australia. However, the population in the Quittner study was from a younger mean age (23.5 ± 9.6 years) compared with this current study (33.0 ± 10.8 years) (Quittner et al., 2012). This may explain some of the variation in the results of treatment burden in our slightly older population. As patients age, increased treatment

requirements may be required to maintain lung function stability. This was discussed by Abbott et al. as greater longevity was at a cost of increased and more complex and onerous daily routines (Abbott et al., 2015).

Although, Quittner et al. had a large cohort of 4,679 adults/teens, all of the domains except treatment burden and health perceptions were comparable with our results (Quittner et al., 2012). In our cohort, participants reported a higher level of treatment burden and lower perception of health compared with the Quittner study. In the Quittner study, a mean of 61.5 ± 21.0 for treatment burden and mean 67.2 ± 24.1 for health perceptions was reported (Quittner et al., 2012). This may be in part due to increased financial provisions in the care of CF patients in Australia where the patients are not reliant on private health insurance for medications. Hence, more treatment including medications and physiotherapy is recommended regardless of patient's insurance status.

Gee et al. (2005) assessed the variables that might be correlated with different domains in the CF QoL questionnaire (Gee et al., 2005). Simple linear and multiple regression analysis using forward selection was used to construct models relating each variable to each HR QoL domain. These authors found a modest positive correlation between FEV_1 % predicted and BMI (r = 0.39) and a small positive correlation between age and BMI (r = 0.27) (Gee et al., 2005). Regression analyses between potential variables (such as FEV_1 %, age and transplant status) and CF QoL domains showed FEV_1 was positively correlated with all HR QoL domains, but this only explained a small proportion of variability. In our study, we found FEV_1 % predicted was positively correlated with all domains other than emotional functioning and concerns for the

future. Patients with a chronic lung disease, such as CF, are highly cognisant of their mortality and for some this can weigh heavily in all of their interactions but for others it does not appear to significantly impact on them.

However, the results of the questionnaires should be interpreted with caution as these particular domains (emotional functioning and concerns for the future) focus on the past 2 weeks and our participants completed this questionnaire during a routine outpatient clinic visit rather than at the beginning or end of an exacerbation. It should be noted as CF is a genetic disease and most of these adults have grown up with the disease, they are likely to be accustomed to its limitations.

Despite our population having a mean FEV_1 % predicted of 64 % indicating a moderate disease severity, the CF participants reported that CF affected their social life minimally (transformed mean score of 82.4) suggesting that it is not solely lung function that contributes to the subject's ability to function as they would like to in the community. There are many other factors including treatment and nutritional regimens that subjects need to adhere to in order to maintain their own level of function.

Patients with greater levels of nutritional intervention or lower BMIs reported a poorer body image in the Gee et al. study (Gee et al., 2005). As previously shown, body image is extremely important to adolescents and adults with CF (Abbott et al., 2000, Walters et al., 1994). However, it is important to note that in a study by Abbott et al., females with CF were happy with their lean body shape, whereas males preferred to be much heavier and bulkier (Abbott et al., 2000). These findings have also been shown in longitudinal studies of CF patients (Abbott et al., 2015). In a society where a slim body

frame is thought to be more desirable for females, our female patients with lower BMI perceive good body image. On the other hand, as discussed above in the study by Abbott et al., and demonstrated in our study, males prefer to be heavier and bulkier and hence if their BMI is at the lower limit of reference range, the males perceive poorer body image compared with their female counterparts (Abbott et al., 2000).

Advancing age, lung function and transplantation are important predictors of outcome across many domains of life quality (Abbott et al., 2015). A longitudinal observational study undertaken by Abbott et al. demonstrated that the treatment burden of CF on patients profoundly impacts all aspects of a person's quality of life and the patient reported QoL declines slowly over time at approximately 1 % per year (Abbott et al., 2015). Further longitudinal research based on our own patient cohort would lead to additional information in this area.

Our response rate was 74 %, better than many previous studies, likely related to the questionnaires being distributed at the time of clinical review by the primary researcher (OE). Response rate from other studies was typically 50-60 % (Gee et al., 2005, Goldbeck and Schmitz, 2001, Walters et al., 1994). The respondents to the UK study differed from our study as only 65% of respondents saw a chest physician specialising in CF. In our study, the respiratory physician attending the CF clinic is a CF specialist and reviews all patients in a dedicated multidisciplinary CF clinic.

A study of 23 adults with CF (61% female), showed that greater than half of the subjects (56.5%) were poor sleepers based on PSQI results and 13% reported poor sleep quality. 19 of these 23 subjects underwent PSG and sleep efficiency was less than 90% in 61%

of these subjects (Iscar-Urrutia et al., 2018). These authors also found a significant correlation between PSQI and all domains of the CFQR 14 (Iscar-Urrutia et al., 2018). Similarly, Bouka et al., found that impaired sleep quality (measured by PSQI > 5) was related to the specific domains of vitality, emotional functioning, social, role, eating disturbances and digestive symptoms in the CFQ-R (German version) (Bouka et al., 2012). These results are in keeping with our results discussed above.

In terms of sleep quality, we found that a lower PSQI score correlated with a higher overall CF QoL score (as shown in Figure 6.6) but we did not find a significant correlation between subjective sleep quality and lung function. In a study of 19 CF subjects with severe lung disease (mean FEV_1 28 ± 7 % predicted) and 10 control subjects, Dancey et al. found that the ESS was within normal limits in both groups (7.3 ± 4.4 in the CF group vs 5.6 ± 4.1 in the control group) (Dancey et al., 2002). These authors did not use the sleep specific QoL measure, PSQI but did use the Mood Profile and Stanford Sleepiness Scale to evaluate mood and daytime sleepiness and found that CF subjects reported significantly lower values for activation domain and happiness as well as reporting a greater level of fatigue when compared with normal subjects (Dancey et al., 2002). The results of the Stanford Sleepiness Scale were not statistically significant between the groups, but the CF subjects showed a trend to greater sleepiness than the control group (Dancey et al., 2002). In our study, which used the well-validated ESS, both in "desaturator" and "non-desaturator" subjects, the ESS was within normal limits in keeping with the data that in CF subjects, sleepiness is reported but not in the abnormal range and subjects may not be aware of excessive sleepiness or have become accustomed to it.

Another study evaluating sleep quality in patients with CF was undertaken by Milross et al., who found that 38% of their subjects (14/37) had a high PSQI (ie. PSQI score > 5) (Milross et al., 2002). The mean PSQI in their subjects was 5.7 ± 4.0 arbitrary units and they found that the areas that contributed most to higher PSQI scores were the questions relating to subjective quality, sleep latency and sleep disturbance (Milross et al., 2002). These results were similar to ours with our mean PSQI reported as 5.9 ± 3.6 and we also found that sleep disturbance, sleep quality and sleep latency all contributed to the higher PSQI scores (where mean was > 1.0 for these domains).

6.6.2 Subjective and Objective Sleep Quality and QoL Data for the Adults with CF undergoing PSG and Sonomat Studies.

Sleep disturbances may be in many forms, external disturbances from bed partners, children, traffic noises or from restless sleep due to leg movements, respiratory events including coughing and arousals post hypopnoeas or apnoeas.

In our study of a subset of CF subjects undertaking an overnight sleep study, we found that nocturnal oxygen desaturation was not associated closely with QoL as measured by CFQ-R. In addition, we did not find that measures of oxygen desaturation correlated with subjective reporting of sleep quality as measured by PSQI findings. It is possible that patients are unaware of their symptoms during sleep so do not report on these on the PSQI. It is only when lung function becomes very severe that patients report issues with their sleep. In a study by Young et al., CF subjects were found to have poor nocturnal oxygenation and this correlated with QoL but was independent of the effect of lung function and awake gas exchange in stable CF patients with moderate to severe

lung disease (Young et al., 2011). Our percentage of "desaturators" (subjects who spent ≥ 10 % of recording time with SpO_2 < 90 %), was comparable with the study by Young et al. who reported that 27% of CF patients in their study had a desaturation of < 90 % for 10 % of recording time (Young et al., 2011).

Comparing those patients who were "desaturators" and those who were not, there was no statistically significant difference on any domain of CF QoL when adjusted for the effects of FEV_1 and awake gas exchange (Young et al., 2011). However, for the most severe group (those spending ≥ 30 % of recording time with SpO_2 < 90 %), the "30 % desaturators" had reduced physical functioning, increased treatment issues and more chest symptoms on the CF QoL questionnaire (Young et al., 2011). These authors also found the "30 % desaturators" had more subjective daytime sleepiness on the ESS and greater exertional dyspnoea on the MRC than non-desaturators (Young et al., 2011) There was no difference in these parameters in the "10% desaturator" group when compared with the non-desaturators (Young et al., 2011). Our patient population had slightly better lung function than the Young et al. population (where FEV_1 was 45 ± 11 FEV_1 % predicted for the "non-desaturators" and 33 ± 13 FEV_1 % predicted for the "10% desaturators" (Young et al., 2011) We did not find any difference between those subjects who desaturated overnight and those who did not in all domains of the CFQ-R, except for the domain of Role Functioning, which may be due to the slightly higher lung function in our subject group. This is in keeping with the fact that the patients with lower lung function are more often away from school / work due to their illness which can often interfere the ability to participate fully in an active life.

6.6.3 Sleep Quality and QoL in a Subset of Adults with CF with Deteriorating Lung Function.

This is the first study to our knowledge evaluating longitudinal subjective sleep quality in CF subjects. In our small subject group with deteriorating disease status, at the subsequent study, total CF QoL was lower but the difference was not statistically significant. We also found that ESS deteriorated slightly but PSQI did not change over time. These results suggest worsening lung function over time was associated with worsening overall QoL. None of the objective parameters of sleep from the PSG between baseline and subsequent studies were shown to be correlated with change in total CF QoL score nor change in PSQI, only the change in ESS was found to be mildly correlated with arousal index. The ESS is a score based on the adult's perception of daytime somnolence which reflects what is happening with increased fragmentation / arousal during the night.

6.6.4 Strengths of the Study

The strengths of this study included assessment of a wide variety of disease severity in patients with CF. Also, the questionnaires were performed during a period of clinical stability or at the end of an exacerbation. We have used CF specific validated questionnaires to assist in assessing disease specific issues that relate to our patients. Analysis of the oximetry data was based on national and international guidelines for nocturnal oxygen therapy and hence these cut-offs of oximetry may be used in future studies of oxygen treatment for CF patients (Beasley et al., 2015, McDonald et al., 2005, Yankaskas et al., 2004).

6.6.5 Limitations of the Study

These studies were performed in a single CF adult centre in metropolitan Sydney. Although, these results cannot be generalised to the entire CF population, in Australia almost all adults with CF attend a specialised CF clinic in a major city. These results are limited to the general CF Australian adult population and the response rate at 74 % may be a bias towards patients who felt they could complete the questionnaire in a positive way or a way in which the physicians wanted at the clinic. Several important variables were not evaluated including the frequency of pulmonary exacerbations, microbiological status, CFRD status, nutritional supplementation status and vascular access status. These confounding factors may play an important role in confirming assessing the true effects of disease variables and QoL.

6.7 CONCLUSION

In conclusion, these studies of adults with CF have demonstrated that overall QoL was strongly correlated with subjective sleep quality as shown by the PSQI. There was no significant correlation between subjective sleep quality or QoL (Total QoL, PSQI or ESS) and lung function. As noted in Chapter 4, objective sleep quality measures (based on the PSG) were not found to correlate with lung function. In addition, the objective parameters of sleep from the PSG were not shown to be correlated with change in total CF QoL score nor change in PSQI between baseline and subsequent studies. However, there was a positive correlation between change in ESS and change in arousal index over time in the longitudinal study. Although, not statistically significant in our subject

group with deteriorating clinical status, subjective QoL measures worsened with worsening clinical status. Further trials are required to assess if other factors play an important role in quality of life for CF patients, or whether any interventions can improve QoL or quality of sleep.

CHAPTER 7: CONCLUSION AND SUMMARY OF RESULTS

This thesis has examined the effect of lung disease in adult cystic fibrosis on sleep and quality of life by using standard PSG measurements of sleep, quality of life and sleep questionnaires, in addition to novel non-invasive sleep and breathing measurement techniques. In adults with CF with clinical deterioration, changes in sleep were systematically assessed to identify abnormalities that may occur over time.

In Chapter 3, it was shown the use of the non-invasive sleep and breathing measurement device, Sonomat, enabled characterisation of respiratory sounds (normal lung sounds, coughs, crackles and wheezes) based on spectrographic and audio analysis. Crackles were identified by short bursts of sound with high amplitude and frequency. Wheezes had a loud musical sound at approximately 400 Hz. In addition to using the Sonomat at a single time point, the Sonomat can also be used longitudinally over a number of days or weeks to identify changes in the above sounds in adults with cystic fibrosis.

In Chapter 4, polysomnography and the Sonomat were used to assess objective measures of sleep in adults with CF. It was found that sleep efficiency, sleep stages and arousal index were similar in our CF population to the non-CF population. However, a high prevalence of mild sleep disordered breathing (RDI > 5 events per hour) was demonstrated. It remains to be seen whether this prevalence is clinically relevant and future larger studies would help in addressing this question. In this study, poorer lung function correlated with lower oxygen saturation both during awake time as well as the nadir oxygen saturation. No correlation was found between poorer lung function and

reduced sleep efficiency, apnoea-hypopnoea index, respiratory disturbance index or arousal index.

The use of the non-invasive device, the Sonomat, in adults with CF was reported in Chapters 4 and 5. The results of the Sonomat demonstrated that the sleep efficiency and AHI were within normal limits for these adults with CF. Subsequent to the identification of respiratory sounds in Chapter 3, it was shown that the Sonomat can be used to detect abnormalities in sleep and breathing that are not measureable using PSG alone. The high percentage of crackles (19.9 % of total sleep time) reported in these adults is consistent with respiratory compromise. In addition, lung function was not found to be correlated with AHI, sleep efficiency or cough. Further, correlations between PSG data and Sonomat data showed that sleep efficiency and AHI were similar for the two recording devices, although RDI tended to be higher for the PSG recording. In addition, there was no relationship between lung function and AHI using either PSG or Sonomat.

In the longitudinal PSG studies reported in Chapter 5, it was demonstrated in adults with severe cystic fibrosis lung disease that sleep efficiency and sleep architecture were within normal limits and that these parameters did not change over time. Although not significant, there was a trend to an increase in RDI and AI over time. In this small subset of adults with CF, overall oxygenation during sleep was reduced at both baseline and subsequent studies. However, only the amount of oxygen desaturation showed a statistically significant increase between the baseline and subsequent studies.

Furthermore, in Chapter 5, the longitudinal effect of deteriorating clinical function on Sonomat sleep parameters was examined. In this small subset of adults with CF, sleep time spent with crackles increased significantly over time (from median 21.8 to 81.7 % of total sleep time). In contrast, coughing or snoring did not change significantly over the time period examined. The need for larger studies examining the effects of deteriorating clinical status is supported by the above results. The finding of increased adventitial sounds in adults with CF might suggest worsening respiratory function over time or signs of an impending exacerbation requiring early intervention to prevent or minimise deterioration.

The quality of life and sleep quality were examined in adults with CF in Chapter 6. The overall QoL strongly correlated with subjective sleep quality (using the PSQI). There was no significant relationship between either subjective sleep quality or QoL with lung function. Furthermore, objective sleep quality measures (arousal index and sleep efficiency) were not related to change in total CF QoL nor change in PSQI. There was a positive relationship between change in ESS and change in arousal index over time in the longitudinal study. Over time, subjective QoL measures tended to worsen with deteriorating clinical status, although this finding was not statistically significant.

In summary, this thesis has used a novel non-invasive measurement device, the Sonomat, to identify respiratory sounds and breathing events in adults with CF. The presence of these sounds during sleep can assist the physician in identifying abnormalities of sleep and breathing. In turn, the physician can use these abnormalities and their clinical acumen to recognise a pulmonary exacerbation earlier and hence intervene earlier to limit or minimise respiratory deterioration in adults with CF.

This thesis also examined quality of life and sleep quality measures and found that overall QoL demonstrated a strong relationship with subjective sleep quality (PSQI) but not with objective measures of sleep quality (such as arousal index, AHI or sleep efficiency based on the PSG or Sonomat) suggesting that qualitative perception of sleep is more important in the overall perception of QoL in adults with CF.

With the advent of novel targeted therapies, it is an exciting time for physicians working in the field of cystic fibrosis. By being able to identify clinical deterioration using non-invasive methods, such as the Sonomat, there is optimism that respiratory deterioration can be further minimised.

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APPENDIX A

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Subject ID:_____ Date:_____

Health
Western Sydney
Local Health District

CFQ-R Cystic Fibrosis Questionnaire - REVISED

Adolescents and Adults (Patients 14 Years Old and Older)

Understanding the impact of your illness and treatments on your everyday life can help your healthcare team keep track of your health and adjust your treatments. For this reason, this questionnaire was specifically developed for people who have cystic fibrosis. Thank you for your willingness to complete this form.

Instructions:

The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Section I. Demographics

Please fill-in the information or tick the box indicating your answer.

A. What is your date of birth?

Date ☐☐ / ☐☐ / ☐☐☐☐

B. What is your gender?

Male ☐ Female ☐

C. During the past two weeks, have you been on holiday or out of school or work for reasons NOT related to your health?

Yes ☐ No ☐

D. What is your current marital status?

- ☐ Single/never married
- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Remarried
- ☐ With a partner

E. Which of the following best describes your racial background?

- ☐ White – UK
- ☐ White – other
- ☐ Indian/Pakistani
- ☐ Chinese/ Asian
- ☐ Caribbean
- ☐ Other (not represented above or people whose predominant origin cannot be determined/mixed race)
- ☐ Prefer not to answer this question

F. What is the highest level of education you have completed?

- ☐ Some secondary school or less
- ☐ GCSEs/ O-levels
- ☐ A/AS-levels
- ☐ Other higher education
- ☐ University degree
- ☐ Professional qualification or post graduate study

G. Which of the following best describes your current work or school status?

- ☐ Attending school outside the home
- ☐ Taking educational courses at home
- ☐ Seeking work
- ☐ Working full or part-time
- ☐ Full time homemaker
- ☐ Not attending school or work due to my health
- ☐ Not working for other reasons

Subject ID:_____ Date:_____

Health
Western Sydney
Local Health District

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Section II. Quality of Life

Please tick the box indicating your answer.

*During the past **two weeks**, to what extent have you had difficulty:*

	A lot of difficulty	*Some difficulty*	*A little difficulty*	*No difficulty*
1. Performing vigorous activities such as running or playing sports				
2. Walking as fast as others				
3. Carrying or lifting heavy things such as books or shopping				
4. Climbing one flight of stairs				
5. Climbing stairs as fast as others				

***During the past two weeks**, indicate how often:*

	Always	*Often*	*Sometimes*	*Never*
6. You felt well				
7. You felt worried				
8. You felt useless				
9. You felt tired				
10. You felt full of energy				
11. You felt exhausted				
12. You felt sad				

Please circle the number indicating your answer. Please choose only one answer for each question.

*Thinking about the state of your health over the last **two weeks**:*

13. To what extent do you have difficulty walking:
    1. You can walk a long time without getting tired
    2. You can walk a long time but you get tired
    3. You cannot walk a long time because you get tired quickly
    4. You avoid walking whenever possible because it's too tiring for you

14. How do you feel about eating?
    1. Just thinking about food makes you feel sick
    2. You never enjoy eating
    3. You are sometimes able to enjoy eating
    4. You are always able to enjoy eating

15. To what extent do your treatments make your daily life more difficult?
    1. Not at all
    2. A little
    3. Moderately
    4. A lot

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

16. How much time do you currently spend each day on your treatments?
1. A lot
2. Some
3. A little
4. Not very much

17. How difficult is it for you to do your treatments (including medications) each day?
1. Not at all
2. A little
3. Moderately
4. Very

18. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

*Thinking about your health during the past **two weeks**, indicate the extent to which each sentence is true or false for you.*

	Very true	*Somewhat true*	*Somewhat false*	*Very false*
19. I have trouble recovering after physical effort				
20. I have to limit vigorous activities such as running or playing sports				
21. I have to force myself to eat				
22. I have to stay at home more than I want to				
23. I feel comfortable discussing my illness with others				
24. I think I am too thin				
25. I think I look different from others my age				
26. I feel bad about my physical appearance				
27. People are afraid that I may be contagious				
28. I get together with my friends a lot				
29. I think my coughing bothers others				
30. I feel comfortable going out at night				
31. I often feel lonely				
32. I feel healthy				
33. It is difficult to make plans for the future (eg. Going to college, getting married, getting promoted at work etc)				
34. I lead a normal life				

Subject ID:_____ Date:_____

Health
Western Sydney
Local Health District

CFQ-R **Adolescents and Adults (Patients 14 Years Old and Older)**

CYSTIC FIBROSIS QUESTIONNAIRE - REVISED

Section III. School, Work, or Daily Activities

Questions 35 to 38 are about school, work, or other daily tasks.

35. To what extent did you have trouble keeping up with your schoolwork, professional work, or other daily activities during the past **two weeks**?

1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

36. How often were you absent from school, work, or unable to complete daily activities during the last two weeks because of your illness or treatments?

☐ Always ☐ Often ☐ Sometimes ☐ Never

37. How often does CF get in the way of meeting your school, work, or personal goals?

☐ Always ☐ Often ☐ Sometimes ☐ Never

38. How often does CF interfere with getting out of the house to run errands such as shopping or going to the bank?

☐ Always ☐ Often ☐ Sometimes ☐ Never

Section IV. Symptom Difficulties

Please select a box indicating your answer.

*Indicate how you have been feeling during the past **two weeks.***

	A great deal	*Somewhat*	*A little*	*Not at all*
39. Have you had trouble gaining weight?				
40. Have you been congested?				
41. Have you been coughing during the day?				
42. Have you had to cough up mucus?				*Go to 44*

43. Has your mucus been mostly:

☐ Clear ☐ Clear to yellow ☐ Yellow-green ☐ Green with traces of blood ☐ Don't know

*How often during the past **two weeks**:*

	Always	*Often*	*Sometimes*	*Never*
44. Have you been wheezing?				
45. Have you had trouble breathing?				
46. Have you woken up during the night because you were coughing?				
47. Have you had problems with wind?				
48. Have you had diarrhea?				
49. Have you had abdominal pain?				
50. Have you had eating problems?				

Please make sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

APPENDIX B

CYSTIC FIBROSIS QUALITY OF LIFE QUESTIONNAIRE

Subject ID_____ Date:_____

The Cystic Fibrosis Quality of Life Questionnaire.

The following questionnaire is designed to find out how CF affects your life. Read each statement, and then indicate which response is **closest to how you feel**, by ticking (√) **one** of the boxes after each statement. Please try to answer **ALL** the questions, **as honestly as you can.**

SECTION ONE:

How often, **over the last two weeks**, do you feel that your CF has affected the following aspects of your physical functioning/mobility?

1. *Because of my CF, **During the last two weeks**, I have had difficulty doing heavy physical jobs. For example, digging, moving furniture, washing the car, vacuuming etc.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

2. ***During the last two weeks**, my CF has prevented me from getting out of the house to run errands. For example, paying bills, posting a letter, doing light shopping etc.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

3. *Because of my CF, **over the last two weeks**, it has been difficult for me to do light tasks around the house. For example, preparing a light snack, washing up, picking up the mail etc.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

4. ***Over the last two weeks**, getting around the house has been difficult because of my CF.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

5. *For the last two weeks, CF has made it difficult to move from my bed or my chair.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

6. *Despite CF, **over the last two weeks** I have got around and done what I like.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

7. *During the last two weeks, there are places that I would like to have gone but didn't because of my CF.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

8. *My CF has limited the type of sports and exercise I have been able to do **over the last two weeks.***

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

9. ***During the last two weeks**, my CF has made me feel lacking in energy.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

10. ***Over the last two weeks****, I have found that my physical functioning and mobility have affected my quality of life by making life less enjoyable.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

SECTION TWO:

Over the **past two weeks**, has CF affected your social life in any of the following ways?

11. *When I have been out socialising,* ***over the last two weeks****, I have behaved more cautiously than I would like to because of my CF.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

12. *Because of my CF,* ***during the last two weeks****, I have tended to avoid visiting friends.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

13. ***For the last two weeks****, I have avoided going out and socialising because of my CF.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

14. *I find that the way in which CF affects my socialising interferes with my overall enjoyment of life.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

SECTION THREE:

The following questions ask you about symptom and treatment aspects of your CF. **How have the following factors affected you over the last two weeks?**

15. ***Over the last two weeks****, I have found my treatments (ie physio, enzymes etc) very time consuming.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

16. ***During the last two weeks****, my treatments have interfered with other things that I have wanted to do.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

17. ***Over the last two weeks****, I have found that my treatments have interfered with my enjoyment of life.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

18. *I have found my breathlessness troublesome,* ***during the last two weeks****.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

19. ***Over the last two weeks**, I have found my coughing troublesome.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

20. *I have found my coughing embarrassing over the **last two weeks**.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

21. *For me, **over the past two weeks**, breathlessness / coughing have made life less enjoyable.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

SECTION FOUR:
Over the past two weeks, I have found that my CF has made me feel:
22. ***Resentful:***

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

23. ***Angry:***

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

24. ***Embarrassed:***

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

25. ***Irritable:***

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

26. *So **fed up** that nothing can cheer me up:*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

*27. **Anxious:***

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never
28. ***Frustrated:***

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

29. *The way that my CF makes me feel **emotionally** interferes with my quality of life.*

☐All of the time ☐most of the time ☐good bit of the time ☐sometimes ☐occasionally ☐ never

PLEASE NOTE, the remaining sections have a slightly different response scale, which asks you to indicate to what extent you either agree or disagree with each statement. Again, indicate which response is the closest to how you feel by ticking (u) one of the boxes after each statement. Please try to answer **ALL** questions as honestly as possible.

SECTION FIVE:

The next section asks you about any concerns that you may have for the future because of your CF:

30. *It concerns me that I may not be able to have any/have more children.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

31. *I have concerns about being assessed for a heart-lung transplant.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

32. *The possibility of needing a heart-lung transplant worries me.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

33. *I worry about CF shortening my life.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

34. *In general thinking about the future makes me feel concerned / worried.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

35. The worries that I have about the future make life less enjoyable.

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

SECTION SIX:

In general , do you agree or disagree that your CF has affected your relationships with other people in any of the following ways?

36. *Establishing new relationships / friendships is difficult because of my CF.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

37. *I find that my friends don't always understand the limits that my CF places on me.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

38. *My CF makes it difficult for me to establish intimate relationships.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

39. *My CF makes it difficult for me to maintain intimate relationships.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

40. *I find that my CF interferes with me having a satisfactory sex life.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

41. *I find that CF makes me feel different from other people my own age.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

42. *My CF makes me feel isolated from other people.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

43. *I am concerned that my CF is stressful for those who are close to me.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

44. *I worry that, because of my CF, I will never be able to lead an independent life.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

45. *The way in which CF affects my relationships with other people interferes with my quality of life by making life less enjoyable.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

SECTION SEVEN:
CF can affect your height/weight, in general how has this made you feel?
46. *I believe that my CF has made me too small.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

47. *I feel that because of my CF I am too thin.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

48. The way that my CF has made me look because of my height / weight makes life less enjoyable.

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

SECTION EIGHT:
The next section asks you about problems you may experience at college, work OR school as a result of your CF. If you are no longer working or at college, please answer the questions in relation to your past experiences.

49. *CF makes/has made, finding a suitable college course/job difficult.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

50. *Holding down a job / college course is / has been difficult because of my CF.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

51. *I am now unable to work / go to college because of my CF.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

52. *I find that CF interferes with my career / college OR school life to such an extent that it makes life less enjoyable.*

☐Strongly agree ☐Agree ☐Slightly agree ☐Slightly disagree ☐Disagree ☐Strongly disagree

Thank you for completing the questionnaire

APPENDIX C

PITTSBURGH SLEEP QUALITY INDEX

The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

APPENDIX D

EPWORTH SLEEPINESS SCALE

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION