The Use of Wearable Technology in Chronic Respiratory Disease

Amar Jitu Shah

22075992

University College London

Research Degree: Division of Medicine

Doctor of Philosophy (PhD)

Primary supervisor: Dr Swapna Mandal

Secondary supervisor: Professor John Hurst

Declaration

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

All the work in this thesis is the candidates, however, the following contribution of work is acknowledged:

1. Chapter 2: A specialised librarian (Mr Alex Stagg) based at UCL helped with the search strategy development. Blind abstract screening and full text review for the systematic review was also undertaken by Dr Malik Althobiani. Dr Chibueze Ogbonnaya, a statistician at UCL helped with the multivariable meta-regression analysis.
2. Chapter 4: the studies were undertaken with some assistance from Dr Anita Saigal. Data analysis techniques were completed under the supervision of Dr Alireza Mani and the network physiology laboratory at University College London.
3. Chapter 5: Part of the data was collected by Ms Nawal Alotaibi. Mr Christopher Reid analysed the sleep study data as the second blinded scorer. Dr Chibueze Ogbonnaya, a statistician at UCL helped with the power calculations.

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My contribution to this thesis was designing the systematic review, the wearable technology survey, and the AcuPebble CPAP study. I was involved in the design of the AcuPebble COPD study with the assistance of my supervisors and Acurable Ltd. I conducted all the studies and performed my own analysis for all the studies. For the AcuPebble COPD study, I was able to develop my coding skills to effectively design and develop codes for the non-linear analysis methodology with the assistance of the network physiology laboratory at UCL. Throughout my PhD I have gained invaluable skills and experience in the appropriate conduct of systematic reviews, clinical trials and statistical analysis methodology. It has been a thoroughly enjoyable experience.

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AJS and SM designed the survey and were responsible for the survey methodology. AJS collected the data for the survey and was involved in the initial analysis of the survey results. AS and MA contributed to further analysis. AJS and SM wrote the initial manuscript, and all authors contributed to the revision and the final approval of the manuscript.

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ERV and SM developed the original methodology for the study together. AJS recruited participants, collected data, analysed data and performed the linear and non-linear analysis with AM. OD helped with trial and device management. AJS wrote the initial draft of the paper AS helped with data collection and data analysis. RP created software to facilitate extraction of the datapoints in a format that facilitate subsequent processing. AJS, SM, AM, JRH made substantial contributions to the interpretation of the data. All authors reviewed and revised the manuscript critically for important

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Abstract

The World Health Organisation has recently recognised a shift towards digital healthcare. Wearable health technology can improve patient self-management, healthcare utilisation and reduce patient morbidity and mortality. Chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) have a global prevalence of roughly 400 million and one billion respectively. The main aim of this work was to investigate the utility of a novel wearable device, AcuPebble RE100, in participants with COPD and OSA. A systematic review and meta-analysis was conducted to initially gain a better understanding of the current landscape of wearables in COPD. This identified a gap, where further research was needed to explore the role of wearables in identifying upcoming exacerbations. The next observational cross-sectional study, sought to build an acceptability model to aid future wearable design to maximise patient utility. The primary study used AcuPebble RE100 in a group of stable and exacerbating COPD patients to analyse physiological signal differences between groups. This observational study demonstrated that heart rate variability increased during an exacerbation, while complexity decreased. Respiratory rate variability and complexity increased during an exacerbation and airflow had increased random fluctuations during an exacerbation. These differences could help build future algorithms to detect upcoming exacerbations, resulting in earlier management initiation and improved patient outcomes. Chapter 5 investigated whether AcuPebble SA100 could be used to monitor patients with OSA on continuous positive airway pressure therapy. This study found AcuPebble SA100 in its current state to be less accurate than gold-standard tools. Overall,

the work in this thesis will help to inform future studies using wearables in chronic lung disease, to positively impact patient outcomes, and lead to a truly digital respiratory healthcare system.

Impact Statement

Wearables have the potential to improve patient healthcare outcomes, but further research is needed to realise these benefits. Earlier detection of an exacerbation of chronic obstructive pulmonary disease (COPD) has been widely recognised as a key research priority. My work has explored the current landscape of wearables in COPD; identified a research gap in exacerbation detection and found that a novel device, AcuPebble RE100, can detect differences between stable and exacerbating COPD participants. I have also investigated the role of wearables in monitoring patients on treatment for obstructive sleep apnoea. My work will have impact in several ways outlined below.

1. My systematic review on wearables and COPD has been published in Nature digital medicine (impact factor 15) and accessed over 3000 times. This work identifies gaps in wearable research in COPD patients, helping inform future studies.
2. My work on wearable technology acceptability shows that patients with chronic lung disease are receptive to new technologies that are highly accurate and easy to use. This work can support small and medium-sized enterprises (SME) in developing wearables specifically targeted at this population. The findings will also be distributed via the Asthma-UK / British Lung Foundation which may help develop future guidance and policies for new wearable designs and inform regulatory bodies on the importance of accuracy.
3. The main body of work highlights key differences between stable and exacerbating COPD patients, this will support development of key

studies that positively impact patient management. By building on work in this thesis and involving SMEs we can develop exacerbation detecting algorithms, that enable patients to start exacerbation management earlier thus improving overall outcomes. This will not only improve patient morbidity and mortality but will also reduce healthcare utilisation and therefore result in national cost savings.

4. While the variability analysis techniques employed in this thesis are well established, their application to a group of patients with COPD is novel and will influence future work. The large amount of data amassed from wearables needs better, meaningful analysis tools, and my work shows this is not only possible but informative. The next focus should be to build on this to create 'normal ranges' for both healthy participants and those suffering from long term lung conditions, such that relevant differences can be established. We also need to understand how the network physiology map differs in stability and sickness, and how we can use variability analysis in the clinical setting to positively impact outcomes in hospitalised patients.
5. My work has highlighted the importance of finding novel tools to accurately monitor patients undergoing continuous positive airway pressure (CPAP) therapy. It has shown that existing wearables that are used to diagnose OSA, need modification to account for CPAP therapy.

The work in this thesis will guide the successful use and application of wearable technology to not only improve patient outcomes but also help to cement their place in a future digital healthcare system.

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CHAPTER 1

1. Chapter 1: Introduction

1.1 Chronic Obstructive Pulmonary Disease

1.1.1 Definition

Chronic obstructive pulmonary disease (COPD) is a heterogeneous long-term lung condition characterised by respiratory symptoms including breathlessness, cough, sputum production and/or exacerbations) which occurs due to abnormal airways and / or alveoli, resulting in persistent and often progressive airflow obstruction. (1)

1.1.2 Burden of COPD

According to the world health organisation (WHO), COPD is currently the third leading cause of death worldwide (2) and in 15 years, COPD is expected to become the leading cause of death, with an economic impact of more than £1.7 trillion (3). A recent systematic review which included 162 population-based studies across 65 countries found that the global prevalence of COPD in people aged 30-79 years in 2019 was 10.3% (CI 8.2-12.8). This roughly equates to 392 million people, the majority of which live in low- and middle-income countries (LMIC). They also found that the prevalence of COPD was higher in men compared to women [14.1% (11.3-17.4%) vs. 6.5% (5.1-8.2%)]. (4)

In the UK, cases have also continued to rise with the British Lung Foundation estimating 1.2 million people currently live with COPD, an increase of nearly 40% from 2011. Furthermore, the National Institute for Health and Care Excellence (NICE) estimates that a further 2 million people are living undiagnosed with COPD, meaning the total burden of disease is likely to be

closer to 3 million. This makes it the second most common lung disease in the UK. (5, 6) COPD also costs the UK economy roughly £1.9 billion each year, causes 115,000 emergency admissions annually, with 16,000 deaths occurring within 90 days of admission. (7, 8) Furthermore, the incidence and mortality are greater in disadvantaged groups, living in areas of low social deprivation where there is a higher prevalence of smokers, poor housing conditions and a greater exposure to occupational hazards. This is resulting in a widening of health inequality and poorer health outcomes. (8)

The burden of COPD is therefore felt both at a patient level and nationally with clearly more research needed to improve overall outcomes and lead to a betterment of patient care.

1.1.3 Aetiology and pathophysiology

COPD results from a complex interplay between host and environmental factors leading to a chronic inflammatory disease process. While cigarette smoking is the commonest environmental risk factor, it is not the only risk factor. Historically it was thought that 15-20% of smokers developed COPD but this is now thought to be significantly higher. (9)

The most common genetic risk factor for COPD is a severe deficiency of alpha-1 antitrypsin (AAT); although in itself it is an uncommon cause of COPD (1% in the UK). (10) In patients with significant reduction (homozygous or heterozygous for the Z- allele) there can be unopposed neutrophil elastase activity and resultant lung damage and COPD. This is further exacerbated by environmental factors such as tobacco exposure. (11, 12) Other potential genetic factors have been suggested based on genome wide association

studies (GWAS), with a recent meta-analysis identifying 82 loci associated with COPD. The genetic interaction and susceptibility in COPD is clearly complex and likely determined by several alleles, rather than one gene. (9)

Lung developmental insults during gestation (e.g., maternal smoking (13)), childhood exposures / infections can affect overall lung growth, leading to a reduced peak lung function and subsequent increased risk of COPD as demonstrated by Lange et al. (14) Moreover, there is some evidence that normal physiological aging bears a resemblance to patients with COPD (enlarged alveolar spaces and increasing loss of lung elasticity), although it is unclear yet if healthy aging alone leads to COPD or it is simply a reflection of cumulative environmental exposures. (15)

Fletcher and Peto (1977) first described the accelerated lung function decline in susceptible smokers, (16) leading to the large body of subsequent evidence describing the causal link between cigarette smoking and COPD development. While cigarette smoking is one of the commonest encountered risk factors for COPD, other types of tobacco, including pipe, cigar and water pipe, as well as marijuana are well described risk factors. (17) Globally, exposure to biomass fumes is an important risk factor in the development of COPD, especially since most COPD deaths occur in LMICs. These countries commonly burn biomass in stoves for cooking and heating. (9)

Occupational exposures are also an important cause of COPD. These include organic and inorganic dusts and fumes. For example, a study of a large UK cohort concluded that certain occupations including gardeners, sculptors and warehouse works were associated with an increased risk of COPD. (18) Furthermore, another cross-sectional study has shown that exposure to

workplace dust is associated not only with airflow limitation but also emphysema and air trapping. (19)

COPD is underpinned by a chronic inflammatory state whereby inhalation of noxious particles including cigarette smoke leads to an amplified inflammatory response that differs from the normal response to respiratory tract irritants. The reason behind this amplified response is not fully understood but host susceptibility and genetics are likely to be at least in part responsible. (17) The main site of airway inflammation and subsequent obstruction is in the small airways. As the severity of this obstruction increases, there is an increased accumulation of mucous and inflammatory cells. The inflammatory cells include macrophages, neutrophils, CD8+ lymphocytes and lymphoid follicles. There is also an imbalance between pro- and anti-inflammatory mechanisms leading to alveolar destruction and emphysema. The severity of airflow limitation is associated with the extent of inflammatory cell infiltration. Once the inflammatory stimulus stops, a reparative process ensues, but some key components of this process are also downregulated in patients with COPD. This adaptive response to either self-antigens or foreign antigens may also explain the persistence of airway inflammation even after smoking cessation. With increasing severity of COPD, bacterial colonisation becomes important and can lead to accelerated decline in lung function and frequent exacerbations, which in turn also accelerate decline. (9, 20)

Lung damage in COPD is also potentiated by oxidative stress. Oxidative stress can be directly caused by cigarette smoke and biomass exposure but also

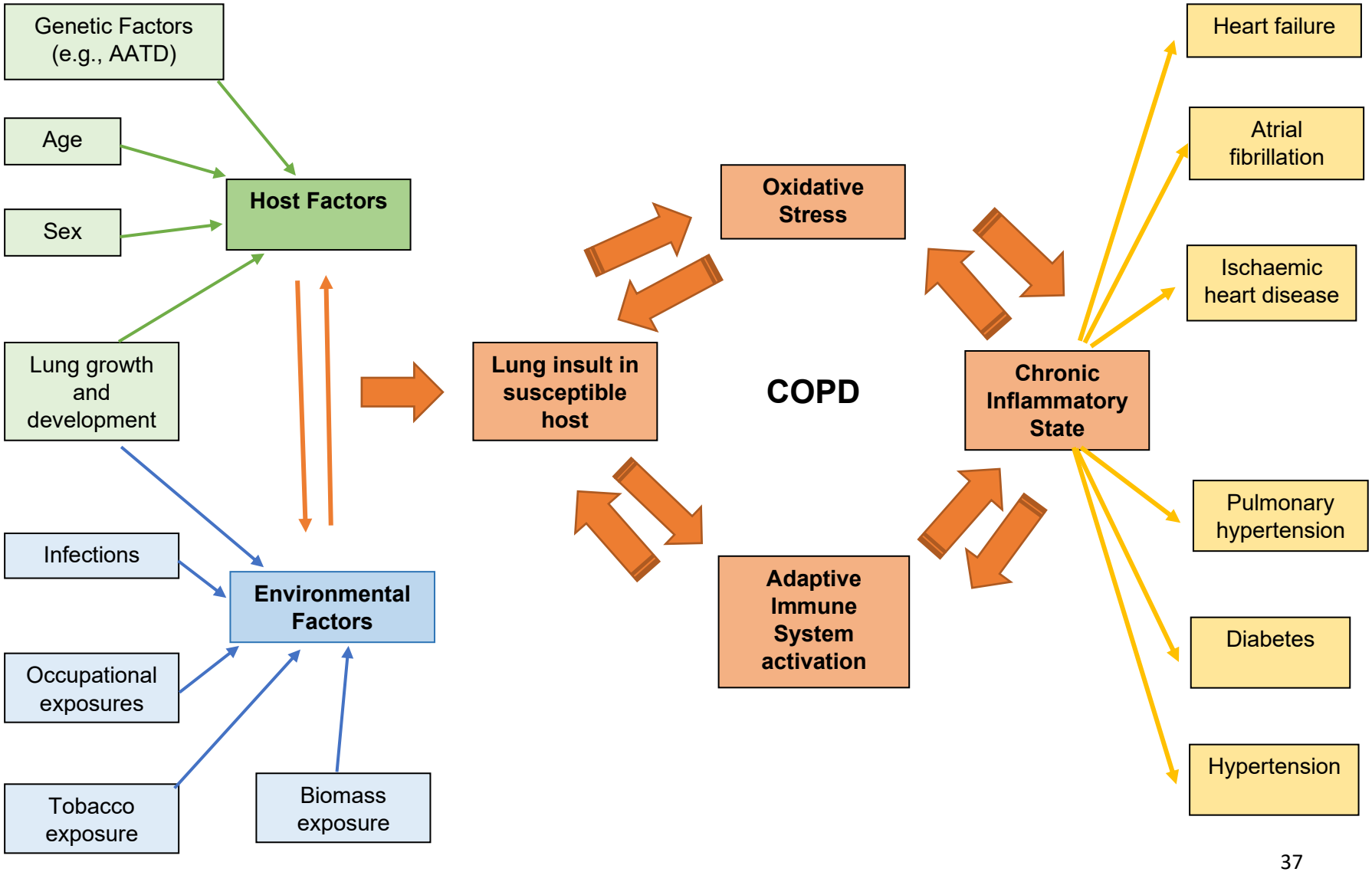
persists in ex-smokers, suggesting that it also rises endogenously. Macrophages release reactive oxidative species resulting in lung damage. Patients with COPD also have reduced antioxidant defences. Oxidative stress results in cytokine and chemokine release causing increased inflammation and activation of MMP9, an elastolytic enzyme which can lead to emphysema. Oxidative stress also impairs the ability of corticosteroids to supress inflammation and directly damages DNA. (21)

COPD represents an underlying chronic inflammatory state and is associated with a large burden of comorbid disease. Mannino et al analysed data from 20,296 subjects and found that impaired lung function was associated with more comorbid disease compared to patients with no impairment. (22) Moreover, cardiovascular disease and COPD share similar risk factors, frequently co-exist and can exacerbate each other with a higher rate of mortality and a higher risk of hospitalisation for both conditions. (23) The fact that COPD is associated with many comorbidities, underpins the idea that COPD can be seen as the pulmonary component of a systemic disease process. (20)

Figure 1-1 summarises the aetiology, pathophysiology and cardiovascular outcomes seen in COPD.

Figure 1-1 Aetiology, pathophysiology, and consequences of COPD

Modified from (17, 20, 21, 23)



1.1.4 Diagnostic criteria

Spirometry is required to make the diagnosis of COPD in an appropriate clinical context where a patient has typical respiratory symptoms and/or an exposure / risk factor history. The presence of a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio of less than 0.7 is the only current way to confirm a diagnosis of COPD. (1) Routine reversibility testing is not recommended as the presence of reversibility does not predict responses to bronchodilators or steroids. However, it is worth mentioning that the FEV1/FVC ratio naturally declines in age and therefore there is a risk of over diagnosis in the elderly population. Furthermore, different ethnicities will also have different normal ranges / cut-offs and is important to bear in mind. While it has been suggested that using the lower limit of normal (LLN) FEV1/FVC ratio may be a better diagnostic cut-off, this has not yet been utilised in both national and international guidelines. (6, 9, 17)

The severity of airflow obstruction in COPD is based on the FEV1% predicted value (all cases requiring a post-bronchodilator FEV1/FVC ratio of <0.7). The NICE guidelines (UK) are now aligned with the international global initiative for chronic obstructive lung disease (GOLD) strategic report, and grade severity as follows: (17, 24)

- **Mild** – FEV1 ≥ 80% predicted.
- **Moderate** – 50% ≤ FEV1 < 80% predicted.
- **Severe** – 30% ≤ FEV1 < 50% predicted.

- **Very Severe** – FEV1 < 30% predicted (or FEV1 < 50%predicted with respiratory failure)

While this scoring system, stratifies patients with regards to airflow severity, it is worth noting that COPD is a heterogenous disease with several different phenotypes, including more traditional ones like emphysema, chronic bronchitis and frequent exacerbators, and newly emerging phenotypes such as the systemic phenotype with a high cardiovascular burden and the non-smoking COPD phenotype. (25, 26) While, there is a weak corelation between FEV1, symptoms and an individual's health impairment, (1, 17) reduced FEV1 has an association with increased mortality. (27)

1.1.5 Management of stable COPD

Appropriate management of COPD requires a holistic and comprehensive assessment of an individual's COPD burden. Given the large degree of heterogeneity and evidence that FEV1 severity alone is not enough to guide management, a more thorough assessment is required. This includes assessing symptoms using validated questionnaires such as the COPD Assessment Tool (CAT) score and MRC breathlessness score, assessing the degree of airflow obstruction (based on the FEV1), and gaining a history of prior exacerbations and the existence of comorbidities. (28)

The Chronic Airways Assessment Test (CAAT)

The Chronic Airways Assessment Test (CAAT) formally known as the COPD Assessment Tool (CAT) score is a short, validated, self-administered

questionnaire, with higher scores indicating increased symptom severity. It consists of eight items which are scored on a six-point scale (0-5) and covers a range of symptoms. It covers several patient symptoms and includes some quality-of-life measures. Furthermore, the initial validation study showed that the items related to cough and sputum production had good discriminative power for milder disease, whereas items concerning chest tightness and confidence leaving the house were more discriminative for severe disease. The remaining items captured moderate disease impairment. (29)

An example of the CAAT score can be seen in Figure 1-2 (taken from Jones et al.) (29)

The CAAT score has very good overall correlation with the COPD-specific version of the St George's Respiratory Questionnaire (r=0.8) and has been incorporated in several guidelines as an assessment, monitoring and severity tool for COPD. (1, 17) The CAAT is also increasingly used in research trials to determine response to both pharmacological and non-pharmacological treatments, such as the effect of pulmonary rehabilitation.

Figure 1-2 Chronic Airways Assessment Test (CAAT) (29)

I never cough	0	1	2	3	4	5	I cough all the time
I have no phlegm (mucous) in my chest at all	0	1	2	3	4	5	My chest is completely full of phlegm (mucous)
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited by doing activities at home
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0	1	2	3	4	5	I don’t sleep soundly because of my lung condition
I have lots of energy	0	1	2	3	4	5	I have no energy at all

For each item in the figure, patients are asked to choose (0-5) which best represents their current situation. Scores overall range from 0-40, with higher scores indicating increased symptom severity.

mMRC Dyspnoea scale

The Medical Research Council (MRC) breathlessness scoring system was first published in 1959 by Fletcher et al to categorise a patient's response to a level of activity. (30) This was modified slightly by Mahler in 1988 to address some limitations in the MRC and provide some more nuanced descriptions of breathlessness. (31) The modified MRC (mMRC) comprises of the following five statements: (32)

0. Breathless only with strenuous exercise
1. Breathless when hurrying on the level or walking up a slight hill.
2. Walks slower than most people of the same age on the level because of breathlessness.
3. Stops for breath after walking about 100 yards or a few minutes on level ground.
4. Too breathless to leave the house, or breathlessness when undressing.

Patients choose the phrase which best describes their current condition. It does not quantify the degree of breathlessness, but rather quantifies the disability associated with breathlessness.

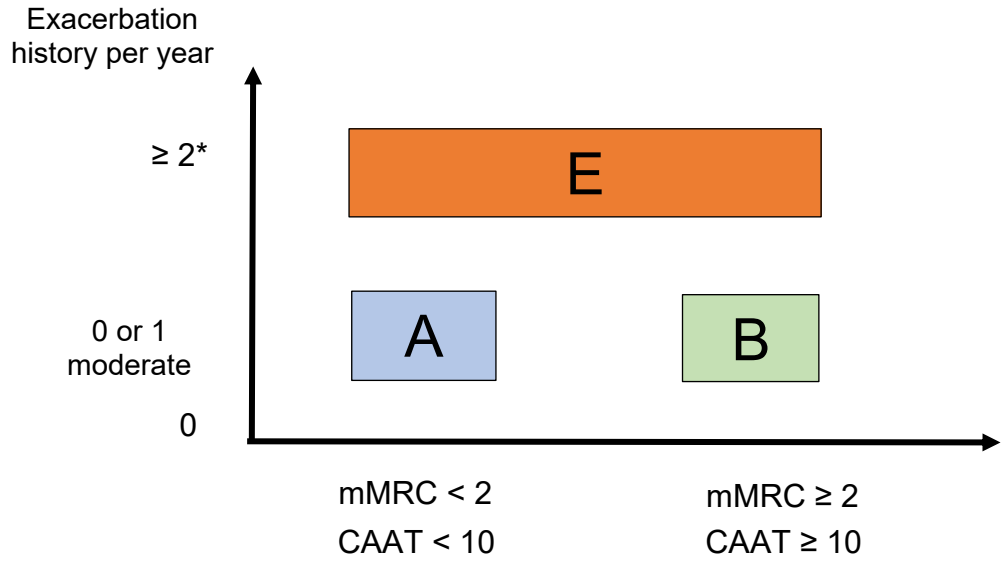
The MRC scale has also been validated as a measure of disability in patients with COPD (33) and is recommended by international guidance as part of the assessment of patient symptom burden. (1)

The GOLD ABE Assessment Tool

The 2023 GOLD strategic report that is updated every year now acknowledges the various phenotypes of COPD and has combined different dimensions of the disease including, symptoms (based on CAAT and MRC scores), airflow obstruction (based on spirometry) and exacerbation frequency to attribute a risk group (A, B or E) to patients. This encourages a more targeted patient management. (28, 34) This is illustrated in Figure 1-3.

Figure 1-3 GOLD ABE assessment tool.

(modified from (9, 34))



*moderate exacerbations or ≥1 leading to hospitalisation. Exacerbations can be classified as mild (an increase in usual inhaled therapy), moderate (requiring antibiotics +/- steroids) or severe (requiring hospital attendance).

The goal in managing patients with COPD is to improve patient symptoms and quality of life as well as reducing their future risk of exacerbations, morbidity, and mortality. Management should be in the form of multidisciplinary teams encompassing community support when appropriate with the patient at the centre of care. The information below is based on UK NICE and the 2024 international GOLD strategic report. (6, 34)

Smoking cessation is of utmost importance and patients should be offered advice and necessary adjuncts at every opportunity. Other non-pharmacological measures include vaccinations (including influenza, pneumococcal, pertussis and COVID-19), pulmonary rehabilitation and nutritional supplementation. All patients should be recommended physical activity and referred to appropriate weight management specialist services if appropriate. Active cycle breathing techniques can also help patients improve their cough and breathlessness.

Medical management is usually in the form of a combination of inhaled therapy that includes bronchodilator agents, and in some cases, inhaled corticosteroids. The GOLD ABE assessment tool is used to try and personalise therapy for different phenotypes of COPD. The initial pharmacological therapy is as follows:

- **GOLD group A** – a bronchodilator should be offered to all patients tailored to its effect on breathlessness.
- **GOLD group B** – Initial therapy is a combination of a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA).

- **GOLD group E** – Initial therapy would be a combined LAMA/LABA inhaler, with consideration of adding in an inhaled corticosteroid if features of airway reversibility on lung function testing, or if blood eosinophils are ≥ 0.3 x 10^9/L, or if they have further exacerbations despite a LAMA/LABA.

The above management represents a change from previous, as inhaled corticosteroids are now used more judiciously given recent evidence that there is an increased risk of pneumonia in this population.

Other add on therapy for patients with COPD who continue to exacerbate may include roflumilast and macrolide therapy and biologic therapy such as anti-IL5 and anti-IL5 receptor antibodies.

Finally surgical management of COPD needs to be considered in some patients and some of the options include lung volume reduction surgery, bullectomy, endobronchial valves and lung transplant.

1.1.6 Acute exacerbations of COPD

COPD exacerbations can be defined as acute episodes where patients experience worsening of their respiratory symptoms, above day-to-day variation, resulting in the requirement for additional therapy. Exacerbations can be classified as mild (an increase in usual inhaled therapy), moderate (requiring antibiotics +/- steroids) or severe (requiring hospital attendance) and are mainly triggered by viral infections. (1) (17) Severe COPD exacerbations are the second largest cause of emergency admissions in the UK. (35) It is well documented that the single best predictor of future exacerbation risk is a

prior history of them. (36) Moreover, the risk of subsequent severe exacerbations is increased threefold after a second exacerbation and 24-fold after the 10th. This clearly significantly impacts patient's quality of life and leads to increased morbidity and mortality. (37)

Aaron et al (2012) characterised the course and pattern of COPD exacerbations in 212 patients using symptom diaries. They found that about half the patients who reported an initial worsening in their respiratory symptoms from baseline crossed the exacerbation threshold (defined as a set higher daily symptom score), whereas the remainder resolved spontaneously following a few days of slightly increased symptoms. Furthermore, they also described two different patterns of exacerbations. The first was sudden onset whereby patients had rapidly increasing symptom burden and shorter recovery back to baseline. While the second was a more gradual onset of symptom severity with a statistically significant longer duration of recovery (OR 1.28, 95% CI 1.06-1.54). (38) They also showed that the time from first onset of increased symptoms to full exacerbation ranged from 0-5 days in 90% of patients, with an overall range of 0-14 days.

Current treatments for COPD exacerbations include antibiotics and oral corticosteroids, coupled with increased inhaled bronchodilator therapy. However, nearly half of all COPD exacerbations are not reported to healthcare professionals. (39) There is also a delay between exacerbation onset and treatment which can lead to poorer patient outcomes. One study found that the median time between exacerbation onset and treatment was 3.69 days

(2.0-5.57). Moreover, the authors of the study also found that failing to report exacerbations led to an increased risk of emergency hospitalisation. (40)

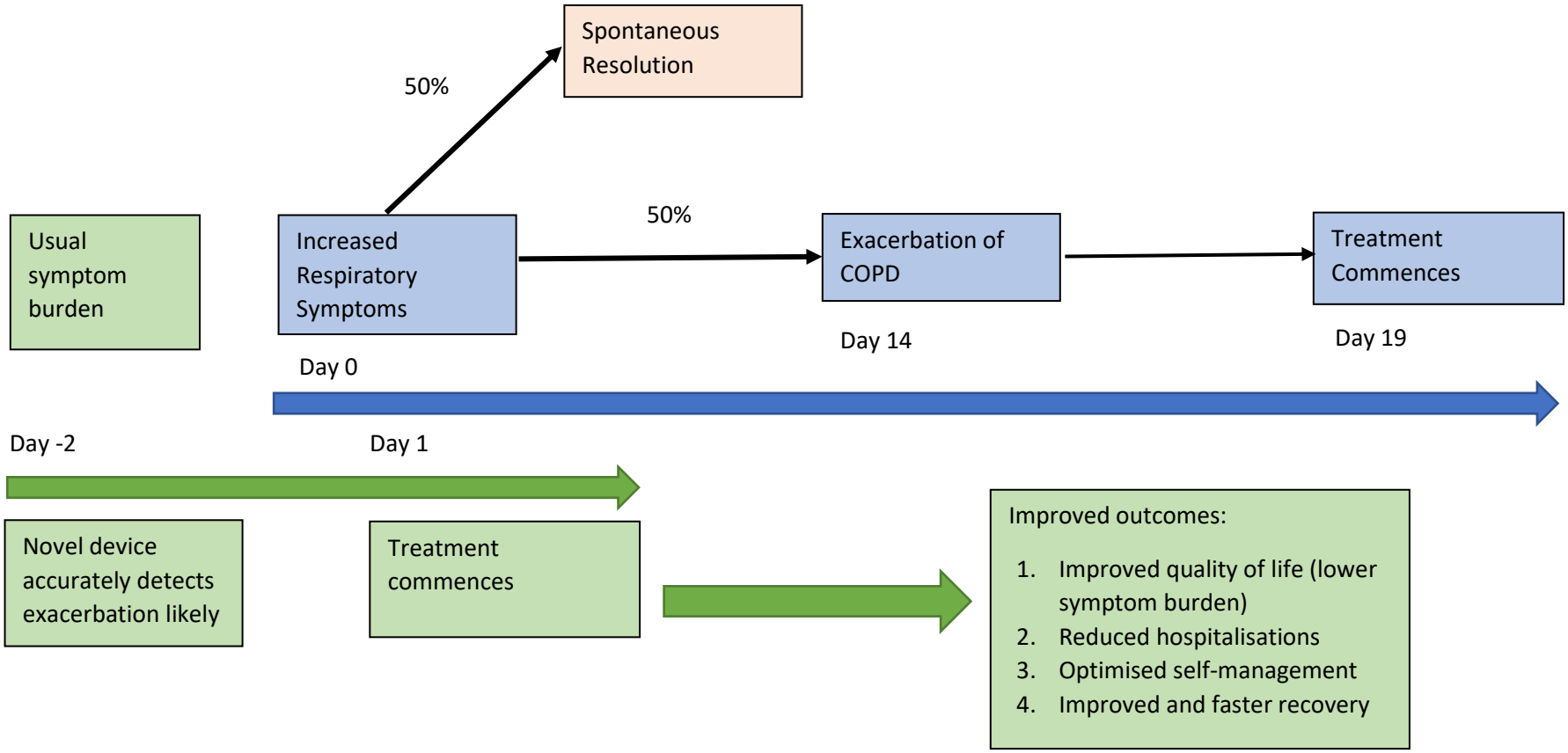
There are several challenges that exist with the current definition of exacerbations. Firstly, there is a sole reliance on patients' subjective perception of increased symptoms, which will vary from patient to patient and can also be affected by patients underlying mental state. Secondly, the symptoms are not related to measurable objective variables that characterise the event itself, and finally severity is only established based on healthcare utilisation. Recently a panel of global experts have established the Rome protocol to try and update the definition and classify the severity of COPD exacerbations by including objective measurements such as respiratory rate, heart rate, oxygen saturations and CRP; but this needs further validation in prospective studies. (41)

It has been widely acknowledged that earlier, and accurate identification of an exacerbation can lead to improved patient outcomes, reducing the risk of hospitalisation and developing respiratory failure. (35, 41) It could also result in cost savings from: 1) reduced emergency hospital admissions; 2) reduced GP visits; 3) reduced work absenteeism and therefore increased productivity. Therefore, finding new predictors/markers of exacerbations is clearly a priority for COPD research. This will enable patients to potentially start their therapy earlier, improving patient outcomes. (35)

Wearable technology, described in detail in Chapter 1.3, is one way of detecting physiological changes before, during and in recovery from an

exacerbation, and can be succinctly defined as a ‘miniature embedded computing system worn by people.’ (42) The potential integration of future wearable technology to enable patients to start and escalate their COPD exacerbation therapy is illustrated in Figure 1-4.

Figure 1-4 The use of wearable technology devices in future exacerbation detection



1.2 Obstructive Sleep Apnoea

1.2.1 Definition

Obstructive sleep apnoea (OSA) is a common sleep disorder, especially in the overweight / obese population, that is characterised by repetitive episodes of partial or complete collapse of the upper airway leading to a reduction or cessation of airflow, resulting in frequent nocturnal desaturations and wakening. (43)

1.2.2 Burden of OSA

The global prevalence of OSA in adults aged 30-69 years is nearly one billion. About 50% of these patients have moderate to severe disease and the largest number of patients are in China, followed by the USA, Brazil, and India. (44) It is estimated that OSA affects about 1.5million patients in the UK, of which a large number (85%) are undiagnosed and therefore untreated. (45) Furthermore, untreated OSA has been shown to decrease quality of life, increase demand for healthcare services and also has a large global economic impact. As an example, a cost-effectiveness study in the USA found that to diagnose and treat every adult in the USA who has OSA it would cost $49.5 billion but the net projected savings would be $100.1 billion. (46)

1.2.3 Diagnostic criteria of OSA

The diagnosis of OSA usually requires typical symptoms and a confirmatory sleep study.

The International Classification of Sleep Disorders 3 criteria for diagnosing OSA require the following: (47)

Either

Symptoms / signs including:

- Daytime sleepiness / somnolence
- Fatigue
- Insomnia
- Nocturnal symptoms including snoring, gasping episodes, witnessed episodes of breathing cessation.

Or

Associated medical / psychiatric disorders including:

- Hypertension
- Coronary artery disease
- Atrial fibrillation
- Congestive heart failure
- Stroke
- Diabetes
- Cognitive decline / dysfunction

- Mood disorder

And

- An overnight sleep study (scored according to the American Association of Sleep Medicine (AASM) criteria) showing ≥ 5 predominantly obstructive respiratory events per hour.

However, it is worth noting that if the overnight sleep study shows ≥ 15 predominantly obstructive respiratory events per hour, patients can be diagnosed with OSA without associated symptoms or medical/psychiatric disorders.

Determining daytime somnolence can be done through the validated Epworth Sleepiness Scale (Appendix 7.7.1) which is an eight-item scale in which patients score the likelihood of falling asleep in various scenarios from not at all (0) to very likely (3). A score of greater than 10/24 is indicative of an increased risk of falling asleep. (48)

Patients can also be referred for sleep studies based on screening tools, such as the STOP-BANG questionnaire, originally developed as a pre-operative screening tool. The STOP-BANG questionnaire uses 8 simple questions / measurements to determine OSA risk: (49)

S – Do you **S**nore loudly?

T – Do you feel **T**ired during the daytime?

O – Has anyone **O**bserved you stop breathing while you sleep?

P – Do you have / are on treatment for high blood **P**ressure

B – Is your **B**MI > 35kg/m^2?

A – Is your **A**ge >50?

N – Is your **N**eck circumference greater than 40cm?

G – Male **G**ender?

One point is given to each of the above points and a score of ≥ 3 is considered to indicate a high risk of OSA.

It is worth noting that while the sensitivities of screening tools tend to be high (98% for STOP-Bang), the specificities are much lower (26% for STOP-BANG). (50) This means a high number of false positive screening tests, which in turn means a large number of patients who are referred for sleep studies, end up having normal studies.

At the Royal Free Hospital NHS Foundation Trust, we screen referrals from general practitioners using a referral questionnaire that incorporates STOP-Bang as well as the ESS and key co-morbidities including hypertension, diabetes, atrial fibrillation, ischaemic heart disease and thyroid disorders. Referrals with an elevated STOP-Bang, associated daytime sleepiness will be triaged for a sleep study.

1.2.3.1 Overnight sleep studies

The diagnosis of OSA is confirmed with an overnight sleep study. There are various categories of sleep studies: (51)

- **Level 1** sleep studies (Reference / Gold standard) – require an overnight stay in a sleep laboratory with a technician in attendance and have a minimum of seven channels of data (usually more than 16), including respiratory, cardiovascular, and neurological sensors.
- **Level 2** sleep studies – the same as level 1 but without a technician in attendance.
- **Level 3** sleep studies – portable home monitors with at least three channels of data (e.g., oxygen saturations, nasal airflow, and respiratory effort). They do not have neurological channels and therefore cannot detect non-respiratory sleep disorders.
- **Level 4** sleep studies – portable devices that capture only one or two channels of data (e.g., overnight oximetry).

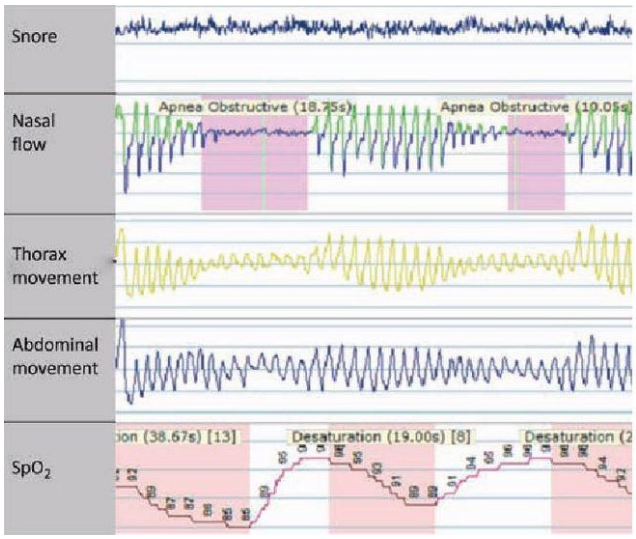
It is worth noting that most sleep studies used in many centres in the UK are level 3, given the ease of testing and portability (for home studies). A systematic review and meta-analysis (n = 59 studies, 5026 patients) comparing level 1 and level 3 studies showed that level 3 studies have good diagnostic performance for diagnosing OSA, with a summary sensitivity between 0.79 – 0.97 and specificity between 0.60 – 0.93 across the different apnoea-hypopnoea cut-offs. (51) Furthermore, the AASM recognise level 3 studies as an acceptable reference standard for diagnosing OSA.

The diagnosis of OSA relies on determining the number of apnoea's and hypopnoea's occurring every hour. This is called the apnoea/hypopnoea index (AHI). An apnoea is defined as a more than 90% reduction in nasal flow lasting

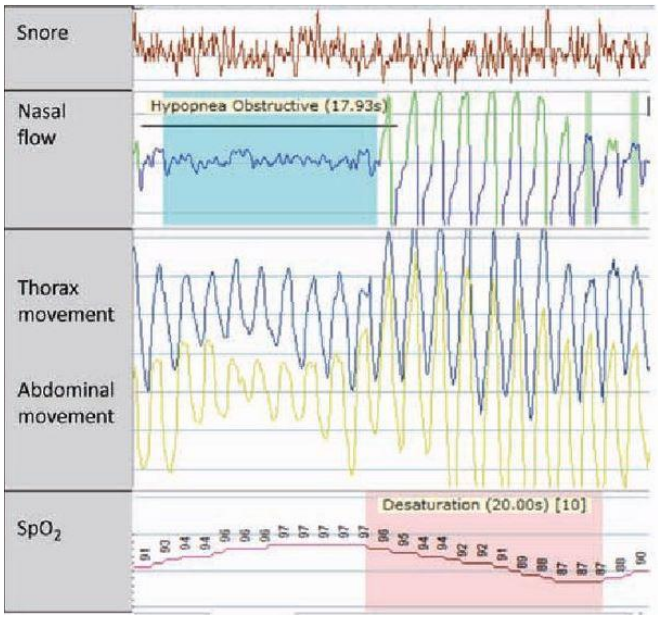
at least 10 seconds, with or without an associated desaturation. A hypopnoea is defined as a reduction in nasal flow by at least 30% lasting at least 10 seconds with an associated 3% or 4% desaturation. For these events to be classified as obstructive, there needs to be evidence of ongoing respiratory effort, in the form of thoraco-abdominal movement. (52) Examples of an obstructive apnoea and hypopnoea are shown in Figure 1-5 below. These have been taken with permission and anonymously from a patient who underwent a sleep study at Royal Free Hospital.

Figure 1-5 Obstructive apnoea and hypopnoea on a multi-channel (level 3) sleep study.

1-5-A: Obstructive apnoea



1-5-B: Obstructive hypopnoea



The severity of OSA is defined by the AHI (number of apnoeas and hypopnoeas per hour):

- **Normal:** AHI < 5
- **Mild:** 5 ≥ AHI < 15
- **Moderate:** 15 ≥ AHI < 30
- **Severe:** AHI ≥ 30

Other useful and relevant information gained from sleep studies include mean nocturnal oxygen saturations and the percentage of time spent with oxygen saturations less than 90%. The latter gives some indication as to whether the patient may have nocturnal hypoventilation and may be a better indicator of hypoxic burden / oxidative stress.

1.2.4 Medical consequences of OSA

Patients with OSA have recurrent episodes of temporary airway obstruction, leading to nocturnal desaturations and arousals. This leads to a surge of sympathetic nervous system activity, resulting in blood pressure elevations, inflammatory mediator release and worsened insulin resistance. Furthermore, the intra-thoracic pressure swings affect pre- and after- load resulting in cardiac remodelling. (53)

A previous literature review (106 articles) concluded that OSA has numerous and serious downstream consequences. These not only include cardiovascular morbidities and hypertension, but also metabolic disorders, cancer and increased perioperative complications. Given patients with OSA

are often somnolent in the daytime, there is also an increased risk of road traffic accidents and occupational accidents. (54)

Table 1-1 outlines some of the major medical consequences of untreated OSA.

Table 1-1 Major medical consequences of OSA.

Medical Condition	**Prevalence / Risk**
Hypertension	Prevalence estimates: 30-50% (55) Pooled odd ratio (OR) for: (56) **Mild OSA:** 1.184 (1.093-1.274) **Moderate OSA:** 1.316 (1.197-1.433) **Severe OSA:** 1.561 (1.287-1.835)
Atrial Fibrillation	OR 2.19 (1.40-3.42) (57)
Heart Failure	Left ventricular ejection fraction significant lower in OSA patients compared to controls (pooled standard mean difference [95%CI] -0.238 (-0.379, -0.097) (58)
Coronary artery disease	Prevalence estimates: 38 – 65% Moderate/severe OSA compared to no / mild OSA had a larger total atheroma volume (461.3 ± 250.4mm^3 vs. 299.2 ± 135.6mm^3) (59)
Cerebrovascular disease	Poststroke prevalence of OSA: 71% (60)
Pulmonary hypertension	Prevalence estimates: 70-80% (55)
Metabolic syndrome	Pooled OR of metabolic syndrome in patients with OSA: 2.87 (2.41-3.42). (61)
Mortality	Severe OSA and all-cause mortality: pooled OR 1.54 (1.21-1.97) (62) Severe OSA and cardiovascular death: pooled OR 2.96 (1.45-6.01) (62) No clear association between mild/moderate OSA and increased mortality risk. (55)
Road Traffic Accidents	Motor vehicle accidents in OSA vs. control: Hazard ratio 1.29 (1.18-1.39). Risk of accidents as pedestrian and bicyclist were not increased. (63)

1.2.5 Management of OSA

The National Institute of Clinical Excellence (NICE), UK has recommended the following treatments, dependant on the severity of OSA and the presence of symptoms. (64)

Mild OSA (asymptomatic / symptoms not affecting activities of daily living)

This group of patients can be managed conservatively with lifestyle measures (such as weight loss, smoking cessation and stopping any sedatives).

Mild OSA (symptomatic)

This group of patients should be offered continuous positive airway pressure (CPAP) therapy. If patients refuse or do not tolerate this treatment, they should be offered a mandibular advancement device. This should be alongside lifestyle measures.

Moderate / Severe OSA (with or without symptoms)

This group of patients should be offered CPAP therapy as first line treatment. However, if they do not tolerate this treatment, they should also be offered a trial of a mandibular advancement device.

CPAP is a machine that blows air continuously through a mask (interface) worn by the patient, splinting open the back of the airway, stopping it from collapsing / narrowing, thus treating OSA.

1.2.5.1 Benefits of CPAP therapy in OSA

Whilst CPAP is considered gold standard therapy for patients with OSA, the benefits on reducing morbidity and mortality are somewhat less clear. There is no doubt that CPAP reduces the AHI, the number of nocturnal desaturations and sleep arousals, thus improving sleep quality. This has also translated into benefits in daytime symptoms of somnolence, quality of life and mental alertness. (43) Furthermore, a recent large Danish cohort study followed 48,168 patients with OSA and concluded that CPAP use was associated with a reduction in motor vehicle accidents [incidence rate ratio 0.75 (0.60-0.91). (63)

However, the benefit with respect to cardiovascular disease outcomes has been mixed. In 2012, Montesi et al undertook a systematic review on the effect of CPAP on blood pressure. They included 28 studies (n=1948) and found that that the weighted mean difference in diurnal systolic blood pressure was -2.58mmHg (-3.57 to -1.59mmHg) in favour of therapy. While statistically significant this is unlikely to be of clinical importance. (65) Following on from this, Iftikhar et al (2014) conducted a systematic review in patients with resistant hypertension and showed a greater reduction in mean systolic blood pressure of -6.74mmHg (-9.98 to -3.49) in favour of CPAP. (66) These results are similar to those of a recent systematic review (2021) published by Labarca et al. (67)

The SAVE trial in 2016 randomised participants with moderate/severe OSA with pre-existing cardiovascular or cerebrovascular disease to receive either

CPAP or usual care alone. Usual care was defined as medical management of their cardiovascular co-morbidities. Their primary composite outcome of interest was death from cardiovascular disease or hospitalisation from unstable angina, heart failure or transient ischaemic attack. They found no significant difference between groups (hazard ratio with CPAP 1.10 (0.91-1.32)). However, they limited their study to a population with an ESS <15, and the mean use of CPAP was only 3.3 hours per night. (68) More recently a systematic review and meta-analysis of 8 randomised controlled trial (n=5684) also found no difference between CPAP and control in the risk of major adverse cardiovascular events (MACE) (risk ratio 0.97 (0.85-1.10). However, subgroup analysis suggested that CPAP was associated with lower MACE (by 36%, p=0.08) in patients who were adherent with CPAP (defined as ≥ 4 hours/night).

With regards to other cardiovascular outcomes (including heart failure, atrial fibrillation, and stroke), the results have also been similar. A recent systematic review also concluded that treatment with CPAP was not associated with a change in fasting glucose. (69) Although a major limitation of most studies has been variable / low concordance with CPAP.

Ideally patients should use their CPAP machine for the duration of their sleep. However, this rarely happens and internationally patients who use CPAP for ≥ 4hours a night for at least 70% of the time, have been classed as adherent or concordant with treatment. (70) Even at this level, studies have shown concordance rates to be between 30-60%. (71) While ≥ 4hours a night is

classified as adherent; this is arbitrary. One study found that differing thresholds of CPAP use were required to achieve significant improvements in sleepiness and daily functioning, beyond which further improvements were unlikely. These thresholds were 4 hours for ESS, 6 hours for the Multiple Sleep Latency Test and 7.5 hours for the Functional Outcomes associated with Sleepiness Questionnaire. The study also found that a significant minority of patients (41%) had an improvement in their ESS with just 2 hours of nightly use. Another systematic review and meta-analysis on cardiovascular outcomes in OSA patients treated with CPAP, demonstrated following sensitivity analysis, that CPAP concordance ≥ 4hours/night reduced MACE by 57% (relative risk 0.43, 0.23-0.80). (72) A small study showed that patients who used CPAP for > 6hours were 7.9 times (p=0.01) more likely to normalise memory function compared to those who used CPAP for < 2hours. Finally, a study investigating mortality in OSA patients treated with CPAP (n = 871) with a mean duration of follow up of 48.5 ± 22.7 months) where 46 patients died, showed that the 5-year cumulative survival rates were significantly lower in patients who did not use CPAP (compliance <1 h) compared to those using the device for >6/d [85.5% (95%CI 78% - 92%) vs. 96.4% (95%CI 94% - 98%), p <0.001)]. A multivariate analysis including compliance, age, arterial hypertension and FEV1 percent predicted showed that that compliance > 6h/day correlated with mortality benefit (OR 0.10 (0.04-0.29)). (73)

It is probable that increasing CPAP use, and concordance will be beneficial to cardiovascular and other outcomes and further studies are required to ascertain this.

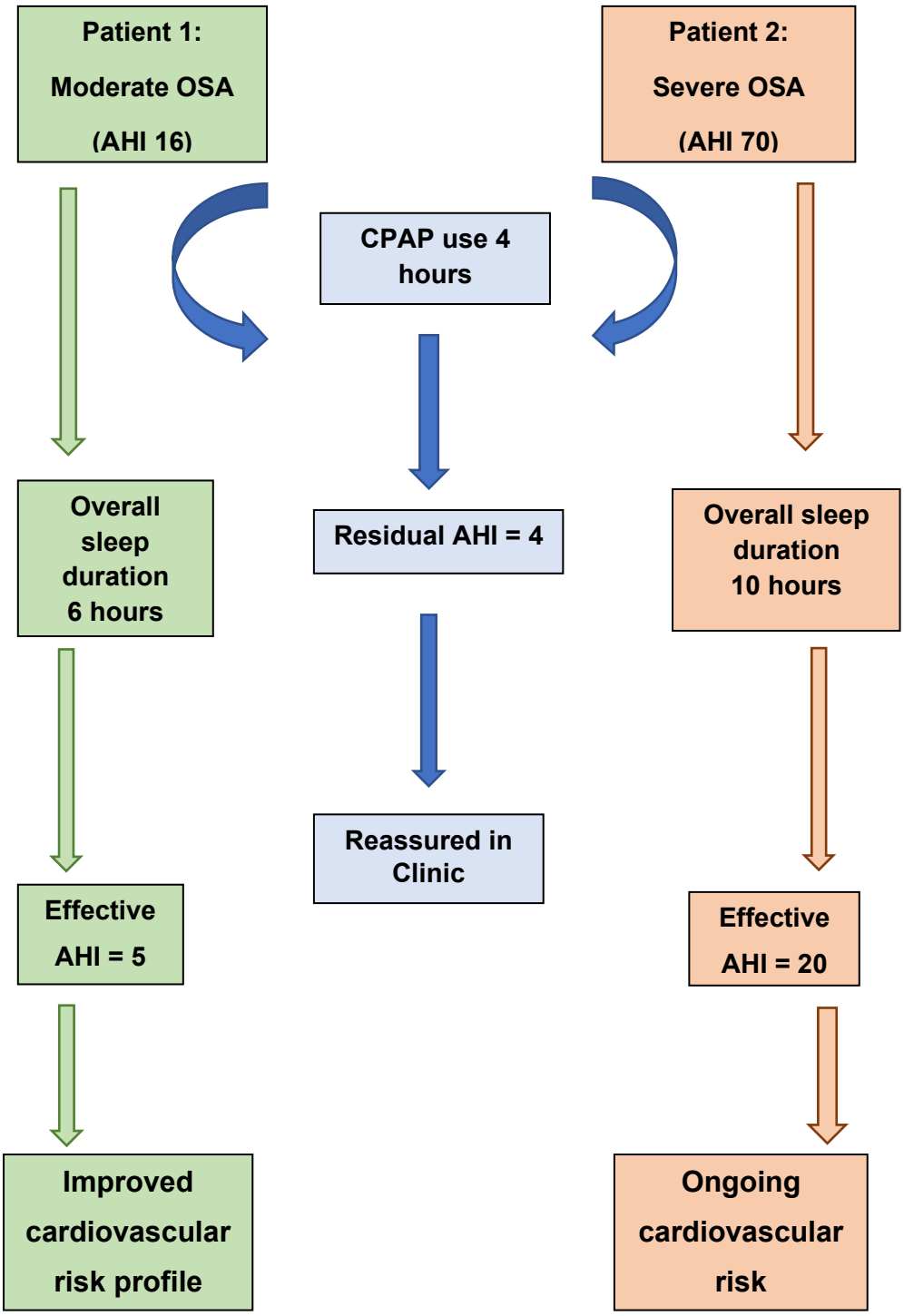
Currently CPAP concordance monitoring in most centres in the UK is conducted via remote telemonitoring, whereby the CPAP machine inherently calculates the residual AHI (i.e., the patients AHI while using the machine). CPAP machines can store airflow and pressure data and thus display to the clinician residual events and compliance indices. However, algorithms between different manufacturers vary and a review by the American Thoracic Society concluded that while usage can be reliably determined, the residual / remnant AHI is not easy to interpret. (74)

Moreover, while machines show the residual AHI, the effective AHI is unknown. The effective AHI was a term introduced by Boyd et al, defined as the 'AHI value measured over the entire sleep period including both the time therapy is and is not being used'. (75) On analysing a small sample (n=28) of severe OSA patients, they found that 63.5% of patients who used CPAP for less than 6 hours still had an effective AHI in the moderate-severe category. This suggests a huge burden of untreated disease. (75)

The data above suggests that a 'one size fits all' approach of recommending > 4hours of CPAP use may not be correct, especially given everyone starts with a differing diagnostic AHI. Further research into accurate ways of monitoring the residual and effective AHI while using CPAP is important as the lack of cardiovascular and other benefits of CPAP therapy may simply be due

to lack of enough use. While 4 hours may be enough for someone who has moderate OSA to begin with, it may not be enough for someone with severe disease or with severe symptoms, or with multiple morbidities, and further work is required to try and provide a patient specific CPAP target requirement. This is likely to overall improve concordance to therapy and lead to morbidity and mortality benefits. This idea is shown in Figure 1-6.

Figure 1-6 Patient specific CPAP therapy target



1.3 Wearable technology

1.3.1 Definition of wearable technology

To understand the definition of wearable technology it is necessary to understand the definition of the following terms first.

A **computer** is an electronic device that processes, stores, and calculates data according to a set of instructions. These instructions are provided by a software or hardware program. A computer therefore can accept data, process it, and compute various outputs depending on the desired outcome. (76)

The **internet** can be defined as an electronic communications network, connecting many different computer networks around the world. (77) The transmission control protocol (TCP) and internet protocol (IP) is a standard set of communication rules which governs how the data is sent across the internet. The internet is a 'packet-switched' network which allows information to be efficiently sent across long distances. The IP sends small 'packets' of information to the right destination and the TCP re-assembles these 'packets' at the receiving end. (78)

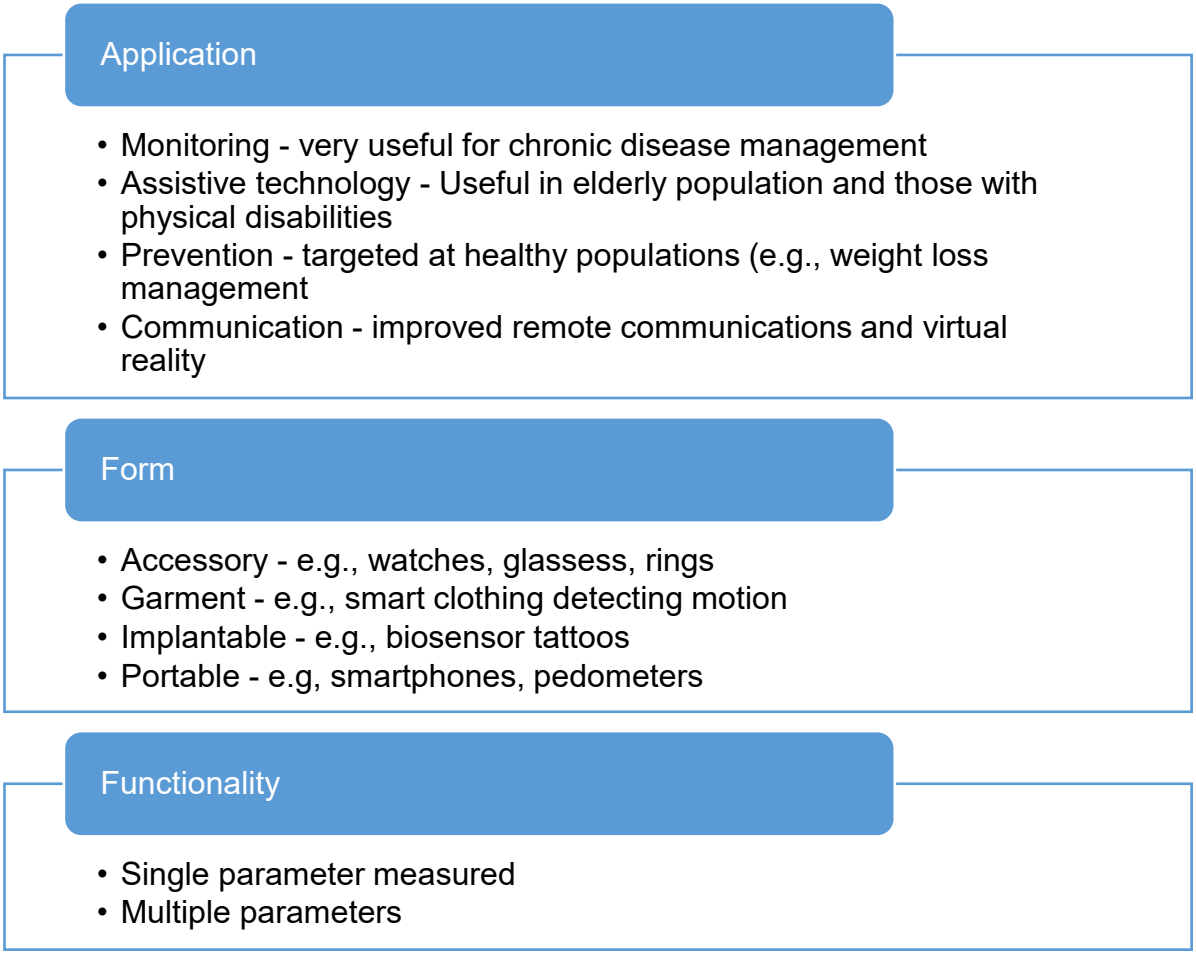
The term **'Internet of Things' (IOT)** was coined by Kevin Ashton in 1999 and can be defined as a network of physical objects. It is essentially a network of different devices ('things') that interact with each other enabling communication between human-to-human, human-to-things, and things-to-things. The sensors embedded in the devices are linked through wired and

wireless networks, often using the same internet IP that connects the internet. (79, 80)

Wearable technology is a leading category of IOT and can be succinctly defined as a ‘miniature embedded computing system worn by people.’ (42) Wearable technology includes any electronic device that is worn close to and/or on the surface of skin or implanted, that can collect, track, monitor and relay information. (81)

In 2015, Alrige and Chatterjee (82) proposed a taxonomy of wearable technology in healthcare, classifying the different technologies according to application, form and functionality. This can be seen in the schematic (Figure 1-7) below.

Figure 1-7 Schematic for the taxonomy of wearable technology in healthcare.



The technical commission 124 of the International Electrotechnical Commission (IEC) similarly categorises four different types of wearable technology: (81)

1. Accessory wearables: low powered devices worn as accessories like smart watches, glasses, or fitness trackers.
2. Textile/Fabric wearables: these are sensors integrated into different textiles.
3. Patchable devices: skin patches which are flexible and thin.
4. Implantable devices: these are implanted in the body.

Furthermore, the IEC further classify these four types depending on their proximity to the body as:

1. Near-body wearables: intended to be near the body but do not need physical contact.
2. On-body wearables: direct skin contact
3. In-body wearables: implanted inside the body.
4. Electronic textiles: fabric-based electronics

1.3.2 A short history of wearable technology

The invention of eyeglasses in 1289 is probably the start of the journey for wearable devices. While a long throw away from the wearable technology we know today it paved the way for other accessories including the pocket watch in 1530, the abacus ring in 1644 and the wristwatch in 1911.

The first wearable computer was developed by Thorpe and Shannon in 1961. They developed a timing device (input) hidden in a shoe that could predict where the ball would land in a game of roulette. The computing device was worn on the waist with feedback output relayed to a speaker behind the ear. (83) Surtherland developed the origins of smart glasses and helmets in the late 1960s, paving the way for augmented reality (AR). (81, 84) In fact AR was not developed until the early 1990's.

The 1970's saw a camera-to-tactile vest for the blind (Smooth-Kettewell) as well as a wearable system to help photographers characterise the way objects responded to light (Steve Mann). (81, 85) Through the 1980s and 1990s, Mann created further wearable technology including a radar system for the blind and audio wearables.

The beginning of the 1990s saw the development of the portable electronic device assistants such as the 'forget-me-not', a continuous recording system enabling users to record their interaction with people. This data was stored on a database for future use. (85, 86) Towards the end of the nineties into the noughties, wearable technology really exploded. Several different wearables developed simultaneously including: the mBraclet™ (1998), a forerunner to

the Apple and Android watches; the Wearable motherboard™ (1999), the first 'smart shirt' monitoring vital signs; the Levi Industrial Clothing Division Jacket™ (2000) contained an internal network designed to interconnect gadgets; the first-ever GoPro camera™ (2004); the Nike and iPod Sport kit'™ (2006) which was a device measuring and recording distance travelled with the aid of a small accelerometer; the Fitbit™ (2007), the first wireless activity tracker to synchronize data with the internet; the Samsung smart watch™ (2009) and Google's Project Glass™ in 2012 was a milestone in augmented reality. (85)

Android wear was developed in 2014 and was the first operating system specifically designed for wearables, mainly smartwatches. (87) Apple inc™ made its first entry into the wearable watch market in 2015. (85)

The above information provides a brief insight into the development of mass, commercially available wearable technology which is now expanding exponentially. However, it is worth noting that several routine medical wearable devices are currently being used in the hospital setting. The following are some common examples:

- Cardiac pacemakers, developed in Stockholm in 1958, were the first implantable medical devices. Further developments and modifications led in 1980 to the multifunctional pacemaker, more akin to what is used today. (88)
- Pulse oximetry, an invaluable tool to monitor patient saturations and heart rate was initially developed in Japan in 1972. (89)

- The electrocardiogram (ECG) has its origins in 1901, where a Dutch physiologist first developed an ECG for clinical use. (90)
- While blood pressure monitors have the origins in the late 19th and early 20th centuries, they are in wide use currently both in hospital and also has home wearable devices. A recent standard published by the Institute of Electrical and Electronics Engineers (IEEE) has published a standard for wearable cuffless blood pressure monitoring. (91)

Mass produced and commercially available wearable technology, emulating bulkier technology used in the hospital setting, is likely to significantly improve patient outcomes. Health wearable technology could potentially improve patient monitoring and diagnostics, as well as lead to increased patient physical activity and may also help patients adhere to beneficial treatments.

The wearable health technology market has grown exponentially recently with an estimated market value of $29.27 billion in 2017, predicted to rise to $195.57 billion by 2027. (92) There is therefore clearly an increasing consumer demand and interest as more people engage with their own healthcare and as personalised medicine starts to become a reality. This concept has also been endorsed by the World Health Organisation (WHO), who have recognised a shift in healthcare to one where digital healthcare, including IOT, is the future. (93)

However, several challenges still exist of which the biggest is the lack of clear regulation and issues surrounding data ownership and privacy. The next

section focuses on some of the wearable health technology regulations that are currently in place.

1.3.3 Wearable technology regulations

This section focuses on regulatory body requirements for medical wearable devices.

The Medical Device Regulation (MDR) which came into force in April 2017, replaced previous European legal frameworks in place. The MDR defines a medical device as:

"any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following purposes:

- *Diagnosis, prevention, monitoring, prediction, prognosis, treatment of alleviation of disease or disability.*
- *Investigation, replacement, or modification of the anatomy or of a physiological or pathological process*

which does not achieve its principal intended action by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means." (94)

If wearable devices fall under the definition of a medical device (as per the above definition) the next step is to classify the device according to the following:

1. Class 1 (low risk)
2. Class IIa or IIb (medium risk)
3. Class III (high risk)

The next step in the process is to involve a Notified Body. A Notified Body is not necessary for medical devices of class 1 unless they have a measuring function. A Notified Body is an organisation that is designated by the EU to assess the conformity of the medical device, in accordance with the legislation set out by the MDR. This is a complex process and covers all stages from the manufacturing of the product to the clinical evaluation of the product which includes summating currently available literature and collecting clinical data. The level of depth required depends on the class of the medical device.

Once all the necessary steps have been completed the medical device can have a CE marking on the product. This shows that the product complies with EU legislation and confirms that it is valid to be sold throughout the European union. (94-96)

Following Brexit, CE marking stopped being recognised in Great Britain following 30 June 2023. Furthermore, UK Notified bodies could not issue CE certificates and instead became UK Approved Bodies. Medical devices sold in the UK instead now need to have a UKCA (United Kingdom Conformity Assessed) mark. Furthermore, all medical devices also need to be registered with the MHRA (Medicines and Healthcare products Regulatory Agency). The MHRA is ultimately responsible for the conformity of the device and monitoring and the device must also conform to the UK Medical device regulations 2002. Moreover, the MHRA will only accept registration of devices where the manufacturers are based in the UK. (97, 98)

Medical devices in the United States require approval from the U.S. Food and Drug Administration (FDA). The route to market for a medical device can take on average 3-7 years and have a large cost implication. The FDA classifies devices into 3 different groups (similar to the EU and UK):

1. Low risk (Class I) – low risk of illness or injury (e.g., surgical gauze)
2. Medium risk (Class II) – e.g., a suture
3. High risk (Class III) – devices which support or sustain human life or are important to prevent damage to human health.

Class I and II device approvals are more focused on registration, manufacturing, and labelling, often do not require large amounts of clinical data. Most class I devices qualify for an 'exempt status', whereby they do not need proof of safety. Class II devices often must demonstrate they will perform as expected and have to go through a pre-market notification (PMN). This also does not need a large amount of robust clinical evidence. Finally, class III devices require a pre-market approval (PMA) and are the most rigorously tested devices with robust clinical data. (99)

Following this process and depending on the type of device, the FDA gives three different outcomes: (100)

1. FDA registered – all medical devices must be registered with the FDA. This only means that the FDA is aware of the device. They cannot use the FDA logo in marketing or labelling the device. This generally applies to class I devices.

2. FDA cleared – these devices have generally gone through a PMN. This generally means the manufacturer can submit evidence that the device in question is similar to another device that has previously been through a rigorous PMA. This usually applies to class II devices.
3. FDA approved – New medical devices which are not similar to others, or class III devices must undergo a PMA. This is a rigorous process that requires robust clinical trial data.

For clinical trials in Great Britain, all medical devices must be UKCA/CE marked for the purpose they are being used for, unless the study is designed to investigate the performance and/or safety of the device. If the device is not CE marked then notification to the MHRA is required along of course with ethics applications via the Health Research Authority (HRA). (101, 102)

1.3.4 Wearable medical devices and COPD

Wearable medical devices are likely to be integrated into telemedicine in the future, to better patient care. Telemedicine can be defined as “the use of electronic and communications technologies to provide and support health care when distance separates the participants” (103) Part of telemedicine is telemonitoring which allows for real-time transfer of data across a distance. Wearable devices enable this telemonitoring to take place. A recent Cochrane review identified 29 studies on telehealth interventions and remote monitoring in COPD. However, only five of these interventions transferred data, allowing real-time review by health professionals, so called synchronous monitoring, as opposed to store and transfer. The authors concluded that the quality of the evidence was very low but remote monitoring was not beneficial overall, and larger studies were necessary. However, they also found no harm. (104) Another systematic review looking into the role of remote patient monitoring to detect exacerbation rates and reduce acute care use was more positive. It included 91 studies and concluded that remote monitoring can lead to reduced acute care use. However, while the studies were of medium-to-high quality, there was a great deal of heterogeneity in terms of patient groups (e.g., comorbidities), the actual intervention (invasive vs. non-invasive; active vs. passive review) and study differences (all-cause vs. disease-specific acute hospital use). (105) Therefore further research is clearly needed in both the field of wearable technology and the role it plays in telemedicine. It is also important to note, that at present, given the paucity of data and the cost of this technology, telemedicine sits at the top of the COPD value pyramid, with an

estimated value of £92,000 per QALY (quality-adjusted life year). This is significantly more expensive than the influenza vaccination (£1000 per QALY). (106)

There have been several advancements in wearable devices and COPD in recent years. Physical activity monitoring and exacerbation detection have been described in detail in the literature review in Chapter 2. The next section focuses on the most common areas which have seen advancements in wearable technology.

Physical activity monitoring

Physical activity plays a vital role in improving outcomes in patients with COPD. Studies have shown that higher levels of physical activity are linked to a reduction in lung function decline, (107) hospitalisations, (108) and mortality. (109) Furthermore, physical inactivity is linked with poorer quality of life and increased breathlessness. (110) Pedometers and accelerometers are two commonly used motion sensors to objectively measure physical activity. (111)

Pedometers are simple wearable devices that count the number of daily steps. Bravata et al conducted a systematic review in 2007 to investigate whether pedometers improve physical activity in outpatients, (not specific to COPD). They included 26 studies (n=2767) and concluded that pedometer use was associated with an increase in physical activity by about 27% from baseline. Moreover, this was associated with a significant decrease in BMI (0.38, CI 0.05-0.72, p=0.03). Having a step goal (like the 10,000 steps) was an important predicter of increased physical activity. (112)

Accelerometers are more advanced and therefore more expensive than pedometers. They typically measure and store the amount and intensity of movement over time. They can detect movement in uniaxial or multiaxial planes.

A review in 2014 found that several different varieties of pedometer models were available on the market with good test-retest reliability (an intraclass correlation coefficient of 0.94). While one study found good correlation between pedometers and triaxial accelerometers, the accuracy was lower with slow walking or inactivity, commonly seen in COPD patients. At that time the research on COPD and physical activity devices had mainly focused on their reliability and validity. (111)

Mendoza et al (2015) conducted a randomised trial to assess whether pedometers improved physical activity in a COPD population [n=97, mean age 69 years, 61% male, mean (SD) FEV1 percent predicted 66% (19)]. (19). COPD patients took part in a 3-month program comparing a standard arm (encouragement alone) or a pedometer-based programme. The pedometer group had a significant improvement in physical activity from baseline (3080 ± 3254 steps/day vs. 138.3 ± 1950 steps/ day). There were also improvements in the CAT score (-3.5 ± 5.5 vs. -0.6 ± 6.6, p=0.001) and the six-minute walk distance (12.4 ± 34.6m vs. -0.7 ± 24.4m, p=0.02). (110)

Qui et al (2018) conducted a systematic review of 15 studies (n = 1316, mean age 66years, FEV1% predicted 42 – 78%), found that step-counter use in a COPD population increased physical activity compared to controls

(standardised mean difference (SMD) = 0.57 (95%CI 0.31 – 0.84), I^2 0.57). (113)

Another systematic review in 2021 assessed patients' perceptions and experiences of wearing physical activity monitors (including smartphone apps and wearables) in a COPD population. They included 12 studies (n=424) in their qualitative analysis. They developed seven different themes across the study and concluded that overall people with COPD liked using the technology and found it useful in increasing their physical activity level. The review also highlighted some negative experiences including some frustration with inaccurate monitoring, technical issues, and the time-consuming nature of monitoring. Feedback from monitors, goal setting and self-monitoring popular with patients. Overall however, the authors felt that there is limited research exploring views of how people with COPD actually integrate technology in their lives and this therefore is something that needs to be explored in the future. (114) The acceptability of physical activity monitors in this group of patients is important if healthcare practitioners want them to engage with the technology.

Pulse oximetry devices.

Pulse oximetry is a widely used wearable device using an optical method based on a reflection of infra-red light. A large Spanish study (n = 2181) has shown that in patients with COPD there is a high correlation (0.89) between oxygen saturations detected by a pulse oximeter (SpO2) and arterial blood gas measurements. (115) Most studies to date, have focused on continuous overnight oximetry measurements to look for oxygen desaturation in patients

with various cardio-respiratory diseases or with certain symptoms. (116-118) However, the clinical usefulness of this has not been fully investigated. The INOX trial aimed to investigate the correction of overnight hypoxia with nocturnal oxygen therapy, in patients with COPD who otherwise do not meet criteria for daytime LTOT. While underpowered for their composite primary outcome of death from any cause or a requirement for LTOT, the study showed no benefit or risk associated with nocturnal oxygen therapy alone. (119) Therefore, while monitoring overnight pulse oximetry may inform COPD patients that they have a degree of nocturnal hypoxia, if this is not associated with any sleep disordered breathing, there is currently no evidence-based beneficial treatment for this. Therefore, the role of nocturnal oximetry monitoring in COPD needs to be further investigated.

Several studies have also looked at the role of 24-hour oxygen monitoring with varying results. Some studies showed a high frequency of daytime desaturation during activities of daily living, while others showed less frequent desaturation (120, 121). This highlights either the heterogenous phenotypes in COPD or normal day-to-day variations or poor sensitivity of the test. Further work in this field is necessary to see whether pulse oximetry monitoring can translate to clinical usefulness.

A study by Buekers et al (2019) investigated the role of continuous pulse oximetry monitoring over a one-week period. They showed that a high percentage of valid SpO2 data could be obtained through a longer monitoring period with significant fluctuations during the week both during the day and

night. This suggests that longer monitoring may have a role in telehealth and fluctuations in oxygen saturations may highlight clinical relevance. (122)

Finally, more recently there has been interest and research into investigating the complex pattern of variability in SpO2 signals using a network physiology approach, showing that oxygen saturation fluctuations are not random, but have useful information about the wider physiological response to hypoxia. Rajeh et al, recruited 11 patients (FEV1% predicted 48 ± 19%) from COPD clinics, who had a history of one moderate/severe COPD exacerbation in the preceding 12 months. All the patients received a wristband pulse oximeter and wore it overnight. All patients had an exacerbation within the study period and the complexity and variability of their oxygen saturation signals was calculated during an exacerbation and compared to a period of stability. They demonstrated increased complexity and variability in COPD patients undergoing an exacerbation compared to the stable state, while the mean saturations remained equal. (123) Therefore, investigating the beat-by-beat fluctuations in saturations at a microscopic level, may hold the key to determining the starting point of an exacerbation.

Wearables to detect COPD exacerbations.

Patients undergoing COPD exacerbations clearly have a change in symptoms and physiological variables. Detection of these changes by wearable technology is likely to lead to earlier detection of exacerbations and then hopefully an improvement in patient care. In 2010, Hurst et al showed that

changes in heart rate, oxygen saturations and peak flow were significantly different just before and during an exacerbation. (124) Following on from this, the PROMETE study in Spain showed that measuring vital signs on daily basis and peak flow three times a week as part of a home telehealth intervention significantly reduced emergency department attendances (20 vs. 57), the need for non-invasive ventilation (0 vs. 8) and the time to first severe exacerbation of COPD increased from 77 days in the control group to 141 days in the telehealth group. (125)

A systematic review by Rajeh et al in 2015 looked at the value of home physiological monitoring in predicting exacerbations in patients with COPD. A total of 16 studies were included, four randomised controlled trials and 12 cohort studies. Patient heart rate (HR) and SpO2 were monitored in 10/16 studies but 7/10 did not report any statistical analyses for the HR or SpO2. Four studies reported significant changes in HR and/or SpO2 prior to the onset of an exacerbation. It is important to note that most of the studies did not use continuous monitoring but rather isolated daily measurements of HR and SpO2. One study (n = 16, moderate-severe COPD) recorded daily respiratory sounds using a microphone over the suprasternal notch. 25/33 exacerbations were detected 5 ± 1.9 days prior to the onset of the exacerbation. From the systematic review, the authors concluded that while there was some positive signal with regards to physiological signals predicting COPD exacerbations, there was not enough reliable data to draw a firm conclusion. Furthermore, there was a gap from detecting variable changes in a research setting to

implementation in a clinical environment, where there are barriers such as determining alarm thresholds, setting up virtual clinics and participant uptake. (126)

The same group went on to compare whether overnight oxygen saturation monitoring was better than once daily monitoring to detect a COPD exacerbation. They found that prior to an exacerbation there was a significant change in heart rate and oxygen saturation levels. However, they also found that symptoms were elevated about five days prior to treatment initiation and the physiological parameters were not statistically better than detecting an exacerbation compared to symptoms alone.

A group in Taiwan (2021) used a combined approach to predict COPD exacerbations. They performed a prospective study gaining data on patient symptoms, physical activity, heart rate, sleep pattern and home air quality to predict whether a patient will experience a COPD exacerbation in the next seven days using machine learning and a smart phone app. They recruited 67 COPD patients prospectively, with a mean 4-month follow-up period and detected 25 exacerbation episodes. For 7-day prediction of exacerbations, their model had a sensitivity of 94% and specificity of 90.4%. The most important variables in their model were daily steps walked, and daily distance moved. (127) It is worth pointing out that this study combined several parameters (symptoms, physiology, lifestyle and environment) to try and predict exacerbations and in reality this is likely to be costly and cumbersome to many patients. Ideally a simple wearable device that is accurate is

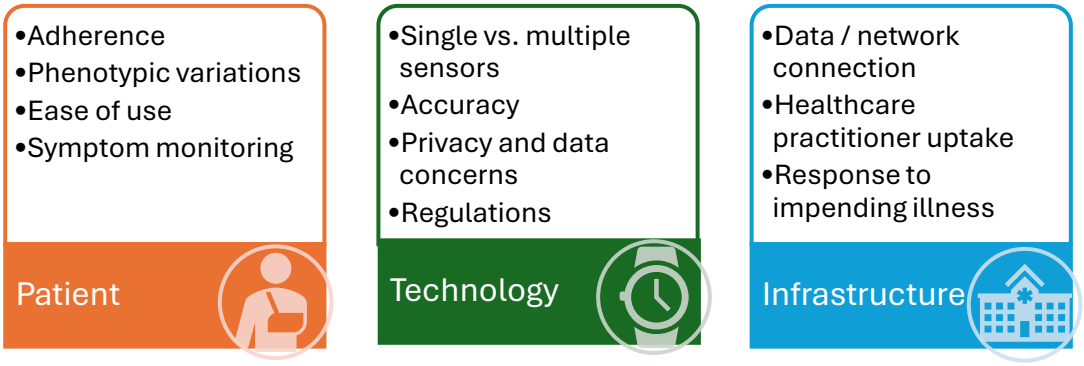
necessary, that objectively predicts an exacerbation, without having to rely on the subjective nature of symptoms.

Studies to date have largely used linear models of analysis when looking at SpO2 and HR traces. However, there is evidence to suggest that these physiological parameters exhibit more complex patterns of variability with multiple different influences. This complex pattern of variability may provide greater insight into exacerbation prediction. Sample entropy looks at the complexity of time series data and can be used to analyse SpO2 and HR traces in a novel way. It measures the degree of regularity vs. irregularity, capturing signal richness or complexity. A more complex signal has increased variability and can be seen as a signal that is more engaged and ready to respond to external stressors. (Appendix 7.1.4) A recent proof-of-concept study showed that during a COPD exacerbation sample entropy increased, even though the mean oxygen saturations remained the same. New wearables could integrate these complex network physiological analyses into their devices, to automate predictions of COPD exacerbations. (123)

Challenges of wearable technology in COPD

Wearable technology is likely to form an integral part of telemedicine in the future but there are several challenges that lie ahead. Figure 1-8 illustrates some of the challenges that remain.

Figure 1-8 Wearable technology future challenges



From existing literature, it is still unclear what the best mode of home monitoring is. Studies have shown symptom monitoring and patient reported outcomes are perhaps as accurate as objective physiological variables. However, objective measurements allow stricter verification of exacerbations. The way in which different phenotypes of COPD and co-morbidities respond to wearables is still unclear and needs further investigation. There is also little research into looking at patient concordance, however, it is likely that a single wearable device is probably going to be better than multiple sensor symptoms. This is especially true if patients lack the ability to use technology. Finally, there are data privacy concerns, health inequalities and digital literacy that also need to be taken into consideration. (128)

Further research into novel wearable devices is needed to improve not only COPD exacerbation prediction but also improve home self-management and optimise COPD care. These devices can ease pressure on an overburdened healthcare system, empower patients to take control of their own health and improve patient outcomes and care.

1.3.5 Wearable technology and OSA

Wearable sleep-trackers have recently exploded onto the consumer market with many products available from wrist watches to armbands and headbands. While there is perhaps a growing recognition of potential benefits of these devices, they largely remain unregulated, with little knowledge on performance. Several devices use actigraphy (using an accelerometer) to measure patters of motion to estimate sleep/wake states. Although the specificity is somewhat limited given, they are unable to differentiate between sleep and motionless wakeful state when compared to gold standard polysomnography. (129)

While several devices exist to try and differentiate different stages of sleep, this section will focus on wearables on OSA specifically. This largely can be split into diagnostic wearables and monitoring/treatment devices.

1.3.5.1 Diagnostic devices:

- *Polysomnography (PSG)* – this is a multichannel wearable sleep study (conducted with or without a technician present), that records several different parameters including brain electrical activity, cardiac and respiratory parameters. The origins of the polysomnography date back to the 1970s and this has become the standardised major gold standard clinical test to diagnose OSA. (130)
- *Level 3 portable home sleep study* – These are portable home sleep study monitors that incorporate cardiovascular and respiratory channels (including oxygen saturations and detection of respiratory /

abdominal effort) but do not record electrical brain activity and thus cannot accurately stage sleep. (131) A large systematic review and meta-analysis suggested good overall diagnostic performance and the AASM recognises these studies as acceptable for diagnosis of OSA. (51)

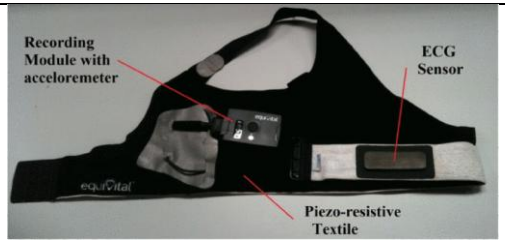
- *Peripheral arterial tonometry (PAT)* devices were first developed in 2000 and subsequently through various iterations are now widely used in the UK for OSA diagnostics. A meta-analysis (2013) of 14 studies comparing PAT devices to PSG showed good correlation of AHI (r=0.889 (0.862-0.911)). (132) These devices are now accepted for OSA diagnosis by the AASM in uncomplicated patients (i.e., those without significant cardiorespiratory disease, neuromuscular disease or suspicion of hypoventilation. (133)
- *Overnight pulse oximetry* – while overnight pulse oximetry (measuring oxygen saturation and heart rate) forms one of the channels in level 1 or level 3 sleep studies, their role in diagnosing OSA is limited and has been shown to have a great deal of variability (specificity 40-100% and sensitivity 30-98%). (134) One study in the UK (n = 89, mean AHI 43), found that if pulse oximetry alone was used to diagnose OSA, 20% of patients with moderate – severe OSA may be missed. (135) It is important to note however, that many studies to date have used linear analysis of oxygen saturation to diagnose OSA, based on the mean saturations and oxygen desaturation index (ODI). However, oxygen saturations represent a complex physiological signal and non-linear

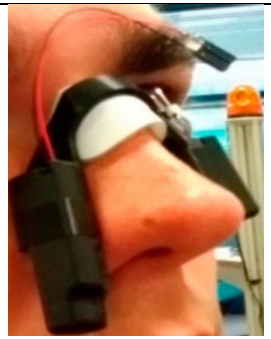
analysis methods may prove to be an interesting avenue to investigate in the future. Furthermore, combining various measures including ODI and other derived variables may improve the overall sensitivity and specificity.

The diagnostic devices described above are those currently in common widespread use throughout the UK. However, recently there have been several other wearable devices that have been explored in the potential diagnosis of OSA. A few of these are outlined in Table 1-2.

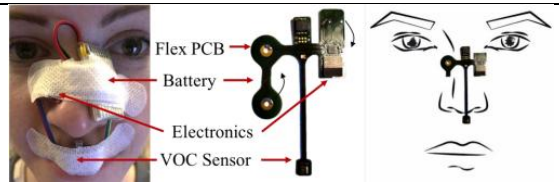
Finally, while not strictly wearable technology, a recent systematic review and meta-analysis investigated the value of a smartphone in diagnosing OSA. Smartphones have various apps and can also link with potentially wearable devices that detect oxygen saturation and heart rate. This review included 11 studies, of which most used either sound or motion to diagnose OSA. All included studies compared smartphones with a PSG. This review concluded that the smartphone diagnostic accuracy had a pooled sensitivity of 90% and pooled sensitivity of 88% for moderate-severe OSA (AHI ≥ 15/hr). The summary AUC was 0.917. The study did, however, find significant heterogeneity between studies. (136)

Table 1-2 Novel wearables to diagnose OSA.

Device sensor type and Name	Picture / description	OSA definition	Comparator	N	Statistical comparison
Wearable Garment (Accelerometer, ECG sensor) Equivital^{TM} EQo2 life monitor (137)		Not specifically used in OSA population	PSG	32	Correlation was observed between respiratory signals, cardiac signals and positional signals. (Nil stats described). Further trials awaited for OSA

Photoplethysmography (PPG) + accelerometer MORFEA (138)		Used in one patient only to detect apnoea's and hypopnoeas. Not specific in OSA	Type 3 sleep study	1	Sensitivity 88.6%, specificity 92.9%
Thoracic and abdominal movement signals analysis from PSG (No specific wearable investigated) (139)	- Analysed 34 existing sleep studies from a database and re-analysed looking at only 2 signals	AHI ≥ 5/hr	PSG	34	Thoracic signals – classification accuracy average 75.9% ± 11.7% Abdominal signals – classification accuracy average 73.8% ± 4.4% Combined accuracy

					81.8% ± 9.4%
Accelerometer – tracheal respiratory movements + deep learning algorithms The Patch (140)		AHI ≥ 15	PSG	69	Using AHI cut-off ≥ 15: Sensitivity 81% Specificity 87% Accuracy 84%
Thermistor (detecting changes in airflow) and galvanic skin response (141)	Nil picture available	N/A	Nil	-	Prototype that sends signals. Needs further validation work.
Airflow and nasal pressure, motion and noise (microphone), accelerometer ARAM (142)		N/A	ResMed ApneaLink Air	6	Needs further work. Unable to provide sensitivities / specificities due to some mechanical

					failures. Further work pending
Volatile Organic Component (VOC) VOCNEA (143)		AHI ≥ 5/hr	Nil	2	100% detection rate from prototype but needs long-term comparison study with PSG
Tracheal sounds and nasal pressure sensor TS-NP PneaVoX TS Sensor (144)	While PSG used, analysis was done using only the combination of oronasal thermister and nasal pressure sensor (Therm-NP)	AHI ≥ 5/hr	Therm-NP	33	Sensitivity when compared to Therm-NP was 93% The authors concluded that tracheal sounds are has good as oronasal thermistors in sleep

					recording systems
Acoustic sensing of physiological sounds (respiratory and cardiovascular) AcuPebble SA100 (145)		≥ 5/hr	Type 3 home sleep monitor	182	Accuracy 95.3% (90.6 – 98.1%) Specificity – 96.8% (91.1-99.3%) Sensitivity – 92.7% (82.4 – 98.0%)

1.3.5.2 Treatment / monitoring devices

- *Positive airway pressure therapy* – CPAP and other positive airway pressure therapy devices such as non-invasive ventilation (NIV) and adaptive servo ventilation (ASV) are devices that are used in the treatment of OSA. Patients wear a mask around their nose and/or mouth which is connected to the device. The device either provides one continuous pressure (CPAP) which splints open the upper airway or provides two different pressures, bilevel. (NIV). These devices can automatically regulate, monitor, and change the pressure according to patient need and therefore are a form of wearable technology. Furthermore, the devices will often connect to a mobile phone app / web cloud to allow information such as usage, leak and required pressure to be recorded and viewed by patients and healthcare professionals. As described above the algorithms between devices vary and there are no standards on how the data should be used and how accurate it is. The American Thoracic Society has concluded that the residual AHI and mask leak will differ between manufacturers and therefore a better, standardised system is necessary to monitor patients on therapy. (74)
- *NightBalance* – This is small device worn on the chest which vibrates when the patient is in a supine position to encourage turning. A randomised study of 110 patients with positional OSA, defined as a supine AHI at least twice the non-supine AHI and at least 30% sleep

time in both supine and non-supine positions, compared auto-CPAP with the positional device showed that while the mean residual AHI post treatment was significantly higher in the positional device arm (7.29 ± 6.8 vs. 3.71 ± 5.1 events/hr, $p<0.001$), the mean AHI difference between the two was 3.58 events/hr (one sided 95% confidence interval 4.96). This showed that for exclusive positional OSA, the device was non-inferior and better tolerated. (146)

The above lists are not exhaustive but shows the variety of different wearable devices that are available / upcoming to aid diagnosis and management of OSA. However, currently only positive airway pressure devices and mandibular advancement devices are approved for treatment of OSA in the UK. We currently do not have a robust way to monitor patients with OSA on treatment, especially given the discrepancies between the residual and effective AHI and so further research into this field is needed.

1.4 AcuPebble – a wearable technology

1.4.1 Acurable Ltd

Acurable is a medical devices company that has offices based in London and Seville. They have developed AcuPebble®. AcuPebble products are wearable acoustic sensors which can continuously record internal body sounds. Signalling algorithms then convert these sounds into various physiological biomarkers including heart rate and respiratory rate.

Professor Esther Rodriguez-Villegas, the founder of the Wearable technologies lab at Imperial College, initially investigated in 2004 whether a small wearable device could monitor apnoea's with the future aim of preventing Sudden Unexpected Death in Epilepsy (SUDEP). In 2014 they studied 20 healthy and 10 patients (referred for sleep apnoea diagnostics) and compared a wearable apnoea detection device (measuring 3.74 x 2.4 x 2.1cm) with an FDA approved level 3 portable sleep study to detect spontaneous apnoeas. The new wearable device had a sensitivity of 88.6% and specificity of 99.6% in the detection of apnoeas. This compared very well with the level 3 device. (147)

Following on from this Professor Rodriguez-Villegas founded Acurable in 2016 to develop further uses for this novel technology. Since then, the company has been awarded multiple industry awards including an Innovate UK grant, and been chosen as a Disrupt 100 company. They passed ISO certification for medical device manufacturers in 2019 and currently have two products. These two products are described below.

1.4.2 AcuPebble SA100

AcuPebble SA100 is a CE marked device for a class IIa medical device as well as FDA cleared as a medical device for OSA testing. The 7g device (shown in Figure 1-8) is circular with a diameter of 2.9cm and height of 1.4cm. It attaches to the neck with a disposable medical grade adhesive. It works by acoustic sensing of physiological sounds, including those generated by the respiratory and cardiovascular systems. It is paired with a self-explanatory mobile phone application. It records acoustic signals from the trachea which are converted by software algorithms to derive breathing segments, respiratory rate, heart rate, airflow and their time-frequency characteristics. These are used to automatically detect disordered breathing events and generate a diagnostic output.

Figure 1-14: AcuPebble SA100

A study conducted at the Royal Free Hospital compared the diagnostic accuracy and acceptability of AcuPebble SA100 with a level 3 portable home sleep device (Embletta MPR Sleep System (Natus Medical, California). While patients were given AcuPebble SA100 face to face, they were not trained on how to use it. A total of 150 patients successfully completed the study.

AcuPebble SA100 automatically generated four different parameters which were compared with polygraphy. The results showed:

- When using standard AASM AHI criteria (with a desaturation threshold of ≥ 3%), AcuPebble SA100 had a sensitivity of 92.4% (82.41-97.98%), specificity of 96.84% (91.05-99.34%) and accuracy of 95.33% (90.62-98.10%) in diagnosing OSA (AHI ≥ 5/hr). Cohen's Kappa was 0.9 (0.82-0.97).
- When using standard AASM AHI criteria (with a desaturation threshold of ≥ 4%), AcuPebble SA100 had a sensitivity of 95.92% (86.02 – 99.50%), specificity 97.03% (91.56 – 99.38%) and accuracy of 96.67% (92.39 – 98.91%) in diagnosing OSA (AHI ≥ 5/hr). Cohen's Kappa was 0.92 (0.86-0.99).
- When using the ODI alone (with a desaturation threshold of ≥ 3%), AcuPebble SA100 has a sensitivity of 91.03% (82.38 – 96.32%), specificity 93.06 (84.53 – 97.71%), accuracy of 92% (86.44-95.8%) in diagnosing an ODI ≥ 5/hr. Cohen's Kappa was 0.84 (0.75-0.93).
- When using the ODI alone (with a desaturation threshold of ≥ 4%), the sensitivity 97.96% (89.15 – 99.95%), specificity 92.08 (84.99 – 96.52%), accuracy 94% (88.92 – 97.22) in diagnosing an ODI ≥ 5/hr. Cohen's Kappa was 0.87 (0.79-0.95).

In terms of usability, 90% of patients found the AcuPebble sensor more comfortable and 97% of patients agreed that it was easier to use. (145)

Acupebble SA100 is now used in clinical practice at the Royal Free Hospital for diagnosis of OSA and has also been selected for the NHS Innovation Accelerator scheme to help support its use throughout the NHS in England.

AcuPebble SA100 is reusable and the per test cost is £50.

1.4.3 AcuPebble RE100

The AcuPebble RE100 is a wearable device that is CE marked for research and is similar to AcuPebble SA100. It also attaches to the base of the neck to record various physiological acoustic signals including sounds generated from patient's respiratory and cardiac functions. These are then wirelessly transferred to a mobile device and uploaded to a GDPR compliant cloud. The device looks exactly like AcuPebble SA100 (Figure 1-14).

Subsequent algorithms convert these sounds into three main physiological signals:

1. Respiratory rate (breaths per minute) measured every two seconds and validation work with Bland Altman plots have shown a RR bias of -0.215 breaths per minute (LOA between -5.747 to 5.316 breaths per minute). (Unpublished)
2. Heart rate (beats per minute) measured every two seconds and the root mean squared error (RMSE) of the heart rate, with the 50-120 beats per minute range is 3.62 beats per minute. (148)
3. Airflow (normalised volt (V)) with a recording every 0.1seconds, giving 100 recordings every second.

1.5. Aims and Objectives

1.5.1 Wearable technology interventions in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis (Chapter 2)

The aim of this systematic review and meta-analysis was to assess the impact of home wearable technology in COPD patients on the following outcomes of interest:

- Physical activity promotion
- Exercise capacity
- Exacerbation detection
- Smoking cessation
- Home self-management
- Disease progression
- Quality of life – assessed by validated scoring systems.

1.5.2 The acceptability of wearable technology for long-term respiratory disease: a cross-sectional survey (Chapter 3)

The primary aim of this cross-sectional survey was to identify the acceptability of wearable technology in a group of patients with chronic respiratory disease.

The secondary aims of the survey were to:

- Identify patient preferences in wearable technology design.
- Identify the impact of social norm perspectives on wearable technology.

1.5.3 Acquisition of physiological signals with a wearable device to assist on research aiming to improve early identification of exacerbations in chronic obstructive pulmonary disease (Chapter 4)

The primary objective of this feasibility and acceptability study was to get physiological signals including heart rate, respiratory rate, and airflow with a small new wearable device (AcuPebble RE100) in a group of stable and exacerbating COPD patients that could be used to objectively differentiate between them.

The aims of this work were:

1. To acquire physiological signals including heart rate, respiratory rate and airflow with a novel small wearable device (AcuPebble RE100) in a group of stable and exacerbating COPD patients.
2. Use linear and non-linear time-series analyses methods to ass the following:
    a. Differences in physiological signal variability between stable and exacerbating COPD patients.
    b. Differences in physiological signal variability amongst patients with different phenotypes of stable COPD patients, specifically looking at:
        i. Airflow severity as assessed by the FEV1 measurement.
        ii. Symptom severity as assessed by validated scoring systems like the COPD Assessment Tool (CAT) and the modified Medical Research Council (mMRC) score.

iii. GOLD ABE categories

c. The association of physiological signal variability measures with currently measured admission characteristics including:
    i. Admission national early warning score 2 (NEWS2).
    ii. The Rome Criteria for COPD exacerbation severity.
    iii. Length of hospital stay
d. Differences in physiological signal variability amongst exacerbating COPD patients at the point of admission vs. discharge vs. post-discharge (i.e., exacerbation recovery).

3. Assess the acceptability and feasbility of the wearable device.
4. Compare the recorded physiological signal measurements from stable and exacerbating COPD patients with a historical non-COPD cohort.

1.5.4 The use of a novel wearable medical device for remote monitoring of patients with obstructive sleep apnoea on continuous positive airway pressure therapy. (Chapter 5)

The primary aim of this study was to determine whether AcuPebble SA100 can accurately determine the residual AHI in patients with OSA on CPAP therapy, using a simultaneous cardio-respiratory polygraphy as the gold standard comparator.

The secondary aims of the study were:

- To determine whether AcuPebble SA100 is more accurate than the CPAP machine in detecting the residual AHI in patients with OSA on CPAP therapy.
- To determine whether AcuPebble SA100 can accurately determine the effective AHI (this includes time spent on and off CPAP, i.e., the whole night).
- To determine whether AcuPebble SA100 is acceptable and comfortable for patients to wear while using CPAP therapy.

CHAPTER 2

2. Chapter 2: Home wearable technology in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis

2.1 Background

Given the significant individual and global burden of COPD, there is an urgent need to find future strategies to improve COPD diagnosis, management, and outcomes for the betterment of patient care. Over the last two decades, there have been several wearable devices that have emerged for the purpose of monitoring patients with COPD, improving physical activity outcomes and preventing exacerbations. However, the reliability, accuracy and utility of the devices are debated, and few have made it into mainstream use.(35)

There have been several previous systematic reviews investigating the role of step-counters, including both pedometers and accelerometers, in promoting physical activity and improving exercise capacity. Qiu et al (2018) identified 15 trials (n =1316) that assessed the efficacy of a step counter in increasing physical activity. They found that step counter use increased physical activity (measured by step-counters) compared to controls (standardised mean difference (SMD) = 0.57 (95%CI 0.31 - 0.84)).(113) Armstong et al (2019) confirmed these findings by reviewing studies looking at pedometer use to promote physical activity either in isolation (n = 12 studies, standardised mean difference (SMD) = 0.53 (95%CI 0.29 - 0.77)) or alongside pulmonary rehabilitation (n = 7studies, SMD 0.51 (0.13 - 0.88)).(149) The SMD is used for comparison of data obtained at different scales / by differing measuring

devices (e.g., different pedometers / accelerometers). It is also used as a balance measure of individual covariates before and after propensity score matching. Both reviews may be biased by including studies that did not mandate gold-standard spirometric diagnostic criteria for COPD and were limited by only including studies investigating step counters. Han et al (2021) also looked at step counter use, but only focused on studies with a duration of at least 12 weeks (n=9) and showed a significant increase in physical activity (≥ 793 steps/day).(150) Finally, Reilly et al (2023) recently reviewed interventions (both wearables and other) to promote physical activity as assessed by step-count in chronic airways disease, but did not split results by different disease groups.(151) Only Qiu et al (113) looked at the effect of step-counters on 6-minute walk distance, and none of the studies looked at the impact of step counters on other physical activity measures, such as time spent at various intensity levels and muscle strength. Moreover, none of these reviews investigated the impact on patients' subjective symptoms and quality of life (using standardised questionnaires).

Patients undergoing COPD exacerbations clearly have a change in symptoms and physiological variables. Detection of these changes by wearable technology is likely to lead to earlier detection of exacerbations and then hopefully an improvement in patient care. In 2010, Hurst et al showed that changes in heart rate, oxygen saturations and peak flow were significantly different just before and during an exacerbation. (124) Following on from this, the PROMETE study in Spain showed that measuring vital signs on daily basis

and peak flow three times a week as part of a home telehealth intervention significantly reduced emergency department attendances (20 vs. 57), the need for non-invasive ventilation (0 vs. 8) and the time to first severe exacerbation of COPD increased from 77 days in the control group to 141 days in the telehealth group. (125)

A systematic review by Rajeh et al in 2015 looked at the value of home physiological monitoring in predicting exacerbations in patients with COPD. A total of 16 studies were included, four randomised controlled trials and 12 cohort studies. Patient heart rate (HR) and SpO2 were monitored in 10/16 studies but 7/10 did not report any statistical analyses for the HR or SpO2. Four studies reported significant changes in HR and/or SpO2 prior to the onset of an exacerbation. It is important to note that most of the studies did not use continuous monitoring but rather isolated daily measurements of HR and SpO2. One study (n = 16, moderate-severe COPD) recorded daily respiratory sounds using a microphone over the suprasternal notch. 25/33 exacerbations were detected 5 ± 1.9 days prior to the onset of the exacerbation. From the systematic review, the authors concluded that while there was some positive signal with regards to physiological signals predicting COPD exacerbations, there was not enough reliable data to draw a firm conclusion. Furthermore, there was a gap from detecting variable changes in a research setting to implementation in a clinical environment, where there are barriers such as determining alarm thresholds, setting up virtual clinics and participant uptake.(126)

The same group went on to compare whether overnight oxygen saturation monitoring was better than once daily monitoring to detect a COPD exacerbation. They found that prior to an exacerbation there was a significant change in heart rate and oxygen saturation levels. However, they also found that symptoms were elevated about five days prior to treatment initiation and the physiological parameters were not statistically better than detecting an exacerbation compared to symptoms alone.

A group in Taiwan (2021) used a combined approach to predict COPD exacerbations. They performed a prospective study gaining data on patient symptoms, physical activity, heart rate, sleep pattern and home air quality to predict whether a patient will experience a COPD exacerbation in the next seven days using machine learning and a smart phone app. They recruited 67 COPD patients prospectively, with a mean 4-month follow-up period and detected 25 exacerbation episodes. For 7-day prediction of exacerbations, their model had a sensitivity of 94% and specificity of 90.4%. The most important variables in their model were daily steps walked, and daily distance moved. (127) It is worth pointing out that this study combined several parameters (symptoms, physiology, lifestyle and environment) to try and predict exacerbations and in reality, this is likely to be costly and cumbersome to many patients. Ideally a simple wearable device that is accurate is necessary, that objectively predicts an exacerbation, without having to rely on the subjective nature of symptoms.

Studies to date have largely used linear models of analysis when looking at SpO2 and HR traces. However, there is evidence to suggest that these physiological parameters exhibit more complex patterns of variability with multiple different influences. This complex pattern of variability may provide greater insight into exacerbation prediction. Sample entropy looks at the complexity of time series data and can be used to analyse SpO2 and HR traces in a novel way. (Appendix 7.1.4) A recent proof-of-concept study showed that during a COPD exacerbation sample entropy increased, even though the mean oxygen saturations remained the same. New wearables could integrate these complex network physiological analyses into their devices, to automate predictions of COPD exacerbations. (123) Recent advances in this field have not yet been subject to systematic review.

To date, reviews have largely focussed on the role of wearables in physical activity metrics and exacerbation detection. However, the management of COPD includes other facets including smoking cessation, quality of life improvement and self-management. None of these have been systematically reviewed. Therefore, it is still not clear, whether home wearable technology can benefit patients with COPD in other aspects of their management. Furthermore, while prior reviews have focussed on step-counters, there may be novel wearable devices that improve physical activity that were excluded from those reviews.

This systematic review and meta-analysis, and therefore some of the figures and tables in this chapter, have already been published in *npj Digital Medicine*

in November 2023 (https://doi.org/10.1038/s41746-023-00962-0) under the creative commons attribution (CC BY 4.0). (152)

2.2 Aims

The aim of this systematic review and meta-analysis was to assess the impact of home wearable technology in COPD patients on the following outcomes of interest:

- Physical activity promotion
- Exercise capacity
- Exacerbation detection
- Smoking cessation
- Home self-management
- Disease progression
- Quality of life – assessed by validated scoring systems.

2.3 Methods

2.3.1 Design

The systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (153) and the Meta-analysis Of Observational Studies (MOOSE) guidelines. (154) The systematic review was prospectively registered at PROSPERO (registration number: CRD42022299706).

2.3.1 Inclusion criteria

- Types of Studies:
    - Studies directly investigating home wearable technology in a COPD population with the pre-specified outcomes of interest, with or without a control / standard of care arm.
    - Randomised controlled trials.
    - Prospective and retrospective observational studies including cohort studies; case-controlled studies and cross-sectional studies.
    - Studies from 1946 onwards
- Types of participants
    - Adult participants with a diagnosis of COPD made with an exposure history, (> 10 pack year smoking history and/or biomass), and post-bronchodilator spirometry showing either:
        - FEV1:FVC < 0.7 or
        - FEV1:FVC < lower limit of normal (LLN)

- Outcomes of interest:
    - Physical activity promotion
    - Exercise capacity
    - Exacerbation detection
    - Smoking cessation
    - Home self-management
    - Disease progression
    - Quality of life measures
- Home wearable technology was defined as any device that was worn/fitted to the subject's body externally which detects and collects data. The device also had to have a means to retrieve the data for analysis e.g., through a computer / smart phone / tablet etc.

3.2.4 Exclusion Criteria

- Studies not in English
- Studies that only used self-reported diagnoses, physician diagnoses or a non-validated questionnaire to diagnose COPD.
- Studies that were narrative reviews, non-research letters, abstracts, case reports, conference proceedings, theses, and books.
- Systematic reviews, meta-analysis, and literature reviews. We did however search reference lists
- Studies involving non-human subjects.
- Studies looking at implantable medical devices.

- Studies looking at in-hospital wearable devices.
- Studies looking at other outcomes of interest.

3.2.5 Search strategy

We searched five databases including: MEDLINE (via Ovid), EMBASE (via Ovid), the Cumulative Index to the Nursing and Allied Literature (CINAHL; EBSCO host), Cochrane Central Register of Controlled Trials (CENTRAL), and the Institute of Electrical and Electronics Engineers (IEEE) Xplore digital library, from inception to April 2023. We used an extensive search strategy which was developed with the help of a specialised librarian and included the terms relating to COPD and wearable technology. The Appendix (Chapter 7.2) shows the search strategies for each of the five databases.

All studies were then uploaded onto EndNote referencing software and duplicates removed by adjusting various filters on EndNote and manually double checking the duplicate entries. The final screening articles were then uploaded onto Rayyan software (available from: https://www.rayyan.ai/). This is an online platform which enables researchers to screen titles and abstracts and mark them for either ‘inclusion’, ‘exclusion’ or ‘maybe’. To increase the internal validity of the screen, a second researcher (MA) also screened the articles in a blinded fashion.

3.2.6 Study selection and data extraction

The initial pool of articles from the search strategy were independently screened by a primary (AJS) and secondary researcher (MA) in a blinded

fashion. The articles were separated into three categories based on this initial screening and the inclusion / exclusion criteria:

- Included
- Excluded
- Maybe

Following the screening of all the articles, the two researchers were unblinded. All the articles in the ‘maybe’ category were discussed to reach a consensus opinion. Full texts at this stage were also read if necessary to aid the decision-making process. The articles in the ‘maybe’ category were either included or excluded based on consensus opinion. When this was not possible, a third reviewer (SM) was asked for their opinion. Any conflicts in the ‘included’ or ‘excluded’ categories were also resolved in the same way. This led to a final list of eligible articles which moved onto the next stage.

Full texts of the eligible articles were reviewed independently by MA and AJS according to the inclusion/exclusion criteria and data was extracted and summated in an excel spreadsheet. The following data from each article was collected:

- General information including main author, year of study, title of study, country of origin.
- Study design
- Date of study collection
- Patient population of interest

- COPD definition / diagnostic criteria
- Population demographics (total number of patients, mean age, sex, COPD severity)
- Name and type of wearable technology intervention
- Duration of use and follow-up
- Primary outcomes of interest
- Secondary outcomes of interest
- Sub-group analyses performed
- Qualitative data with regards to wearable technology
- Quality of the study. The risk of bias assessment was performed using either the modified Newcastle-Ottawa Scale for non-randomised / observational studies (155) or the Cochrane Risk of Bias Tool for randomised controlled trials. (156)

Following on from this a final list of included and excluded studies was confirmed with any disagreements at this stage resolved by a third person (SM).

3.2.8 Data analysis

Meta-analysis

Only objective measurements (e.g., mean daily step count, six-minute walk distance, CAT score, number of exacerbations etc.) that could be grouped together were included in the meta-analysis. Subjective outcome measurements were not included.

All statistical analysis was performed using the Cochrane Collaboration RevMan software (version 5.4) and Rstudio version 4.2.3.

Mean change scores with the corresponding standard deviation (SD) for the objective outcomes of interest were used in the meta-analysis to obtain the overall effect size. This was presented as either the mean difference or the standardised mean difference (SMD) with a 95% confidence interval. SMD was used only where the same outcome measure was obtained by different measurement approaches and devices, e.g., different pedometers measuring the mean daily steps.

Where studies had not given the mean change scores, the mean change score was calculated simply by subtracting the post-intervention mean from the baseline mean. The SD change in this instance was calculated using an imputed correlation coefficient of 0.80, using Equation 1 shown below. This was derived from the Cochrane handbook. (157)

Equation 1: Calculation of SD change using an imputed correlation coefficient of 0.80 (derived from (157))

$$SD_{Change} = \sqrt{SD_{baseline}^2 + SD_{Final}^2 - (2 \times Corr \times SD_{Baseline} \times SD_{Final})}$$

Where studies quoted mean with standard error or confidence intervals, these were changed to mean and SD using RevMan software.

Heterogeneity was assessed by the I^2 value. A value ≥ 50% was indicative of significant heterogeneity and in this instance a random-effects meta-analysis model was employed compared to a fixed-model.

To understand the sources of heterogeneity between studies, a multivariable meta-regression analysis was conducted with five covariates, age, publication year, FEV1%predicted, type of wearable used as part of the intervention and the outcome measurement device. A mixed effects meta-regression was performed using a Knapp-Hartung modification, and the overall model fit assessed by the Bayesian information criterion.

If appropriate, subgroup analyses were also performed looking at the effect of the type of intervention (e.g., isolated wearable, wearable with additional health coaching or pulmonary rehabilitation), duration of wearable use, outcome measurement device (pedometer vs. accelerometer) and severity of COPD (moderate vs. severe).

Where meta-analysis was not possible due to significant heterogeneity, a narrative synthesis was conducted based on the Cochrane Data Synthesis and Analysis guidelines, and outlined the following:

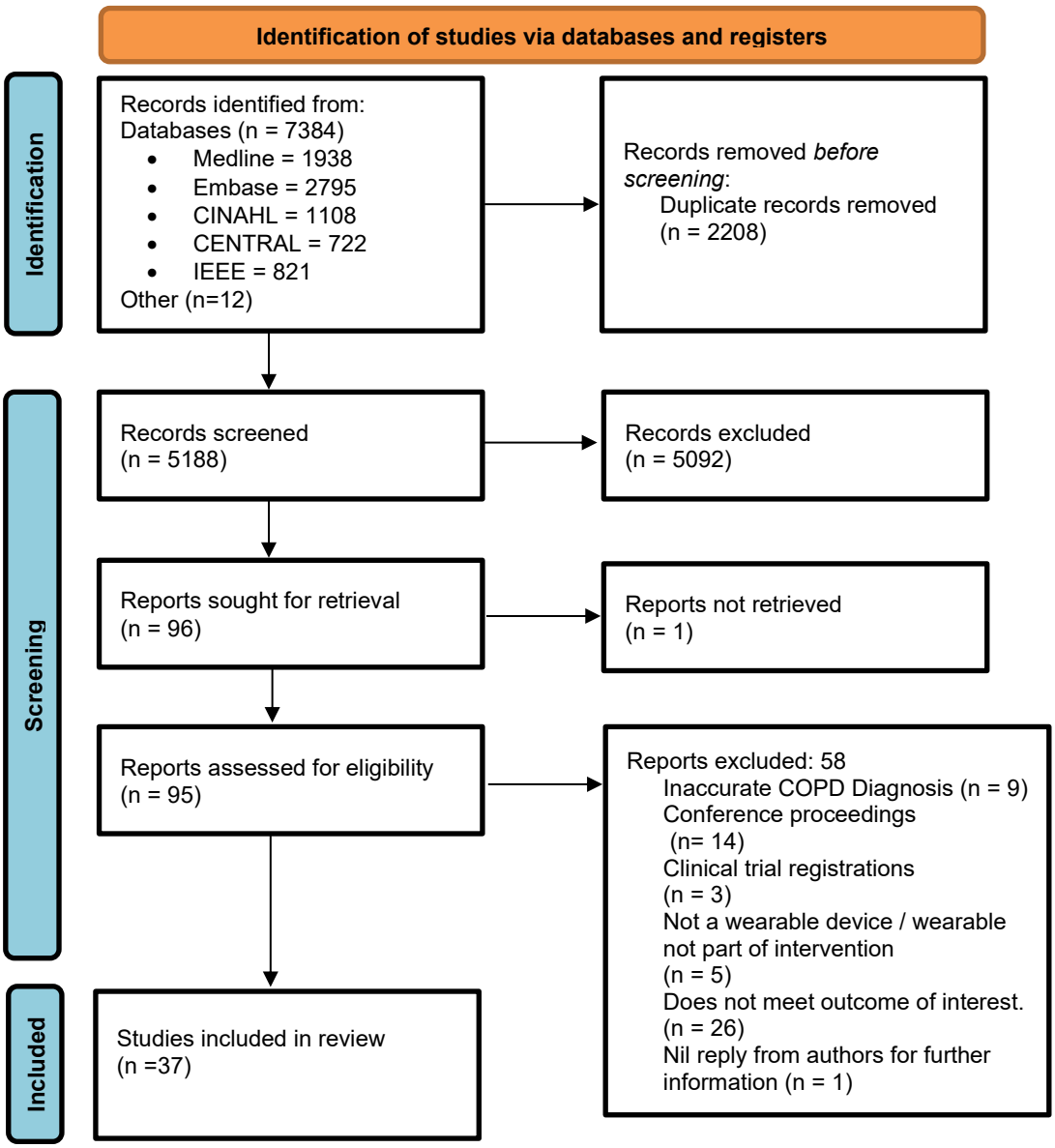
- A description of the included studies was summarised and tabulated. We commented on study type, type of wearable technology, methodology, main outcomes of interest and risk of bias. This was grouped by the outcome of interest.
- Similarities and differences between the included studies.
- Details of the studies based on the outcome measures outlined below.

- Relevant statistical tests when wearable technology was compared with standard of care.

2.4 Results

The initial search generated 7396 potential studies of which 2208 were immediately excluded due to duplication. After the first screening of titles and abstracts, 96 studies were sought for retrieval, but one study was inaccessible, and the author was not reachable. Therefore, 95 studies were assessed in full for eligibility according to our inclusion criteria. An additional 58 papers were excluded following full-text review. A total of 37 studies were analysed. Figure 2-1 shows the PRISMA flow diagram. The list of excluded studies with reasons for exclusion can be seen in Appendix (Chapter 7.3).

Figure 2-1 PRISMA flow chart for included studies.



2.4.1 Characteristics of included studies.

A summary of the included studies can be seen in Table 2-1. Thirty studies (158-187) investigated the role of wearable technology in improving physical activity outcomes (27 randomised controlled trials (RCT) (162, 163, 165-173, 175-178, 180-187) and three observational studies (164, 174, 179)). These studies included 2955 patients (69% male) with a median (IQR) sample size of 53 (32 – 143), mean (SD) age of 67 (6) years and a median (IQR) FEV1% predicted of 54% (45 – 59%). For the RCTs the median (IQR) drop-out rate in the intervention group was 20% (10% - 29%), similar to 17% (10% - 28%) in the control group. The majority of RCT's used a per-protocol analysis (80%).

Ten studies (123, 127, 159, 177, 178, 188-192) investigated the role of wearable technology for COPD exacerbation detection (six RCTs and four observational studies). The studies included 3660 patients (69% male) with a median (IQR) sample size of 78 (46 – 143), mean (SD) age of 69 (2) years and a median (IQR) FEV1% predicted of 57% (53 – 61%). For the RCTs the median (range) drop-out rate in the intervention group was 36% (9% - 56%) and was 17% (4% - 30%) in the control group.

Quality of life measures using validated scoring systems were secondary outcome measures in 24 (159, 160, 162, 163, 165-178, 180-182, 184, 185, 187) of the 30 studies that were investigating the role of wearable technology in physical activity measures. The median (IQR) duration of these studies was 5.4months (2.9 – 6months)

Two studies (162, 177) investigated whether wearable technology was associated with improved self-management, although they both used different scoring systems.

There were no studies investigating the other outcomes of interest.

Table 2-1 Characteristics of included studies.

Author, Year, Country	Study Design	Sampling / N / Duration of intervention / COPD Severity	Intervention Group / wearable used / sample characteristics / Attrition rate	Control Group / sample characteristics / Attrition rate	Outcomes of interest	
					Outcome measure	Mean difference between groups (95%CI) from baseline to end of study duration Or Other difference measure
Al Rajeh et al 2020 UK (188)	RCT Per Protocol	Stable COPD patients	Overnight pulse oximetry measurements (SpO2 and HR). Recorded every 4 seconds	Once daily measurement of HR and SpO2	Exacerbation detection using changes in HR and Saturations	Control group showed no statistically significant variation from baseline prior to an exacerbation. Intervention group showed significant variation from baseline for both heart rate and oxygen saturation pre-exacerbation.
		88 randomised 44 to intervention 44 to control	Nonin 3150 pulse oximeter			
		6 months or 1st exacerbation	Exacerbated N = 13; Male = 7 (54%) Mean age ± SD = 71 ± 3	Exacerbated N = 14; Male = 4(29%) Mean age ± SD = 72 ± 3	Composite score (of changes in heart rate and oxygen saturations)	Composite score increased in control group for 1 day prior to exacerbation. Composite score in intervention group increased for 7 days prior to exacerbation with a positive predictive value of 91.7%; sensitivity 84.6% and specificity of 81.8%
		FEV1% 52.9	Attrition rate: 52%	Attrition rate: 59%		
Al Rajeh et al* 2021 UK(123)	OBS	Stable COPD patients	Overnight pulse oximetry measurements (SpO2 and HR). Recorded every 4 seconds. This is secondary analysis of Al Rajeh et al (2020) described above	-	Oxygen saturation variability measures	Data presented as stable phase vs. exacerbation phase.
					Mean SpO2 (mean (SD))	91.4 ± 1.89% vs. 90.6 ± 2.11%; p=0.125
		13	Nonin 3150		Sample entropy	0.395 ± 0.101 vs. 0.505 ± 0.159; p=0.029
		1st exacerbation	N = 11; Male 7 (64%) Mean age ± SD = 72 ± 10		DFA (α1)	1.17 ± 0.110 vs. 1.15 ± 0.137; p = 0.555

		FEV1% 47.7	Attrition rate: 15%		DFA (α2)	1.04 ± 0.114 vs. 0.925 ± 0.107; p = 0.002
Altenburg et al 2014 Netherlands (158)	RCT Per Protocol	Stable COPD patients from both GP practices, secondary care and PR	12-week lifestyle physical activity counselling programme. Pedometer with feedback and motivation and 5x30min counselling sessions for 3 months.	Usual Care	Median Daily Steps	Median (IQR) daily step change given: Intervention 218 (-1423 to 1863) Control -201 (-1809 to 1006)
		155 randomised 78 to intervention 77 to control	Digiwalker SW-2000, Yamax, Tokyo, Japan		6MWD (m)	Median (IQR) at each time point given Intervention: Baseline: 454 (361 to 509) 15-months: 506 (422 to 571) Control: Baseline: 450 (351 to 530) 15-months: 468 (417 to 543)
		15months	Demographics only given for whole groups: N = 155; Male 102 (66%) Median age (IQR) = 62 (54-69)	Demographics only given for whole groups: N = 155; Male 102 (66%) Median age (IQR) = 62 (54-69)		
		FEV1% 60	Attrition rate: 36%	Attrition rate: 34%		
Arbillaga-Etxarri et al 2018 Spain (159)	RCT Per Protocol	Stable COPD patients	'Urban Training intervention' – motivational interviewing, urban training walking trails, walking groups and a pedometer	Usual care – general health counselling and ELF information brochure (recommending ≥ 30min moderate physical activity ≥ 5days/week	Mean daily steps	-136.00 (-768.20 to 496.20)
		407 randomised 202 to intervention 205 to control	Onstep 50 Geonaute and Omron Pedometer		Severe COPD Exacerbation (%)	Mean difference of 6% (control group 3% and intervention 9%)
					6MWD (m)	-3.00 (-17.13 to 11.13)
		12 months	Analysed N = 132; Male = 114 (86%) Mean age ± SD = 68 ± 9	Analysed N = 148; Male = 130 (88%) Mean age ± SD = 69 ± 8	CAT Score	0.00 (-1.08 to 1.08
		FEV1% 57	Attrition rate: 35%	Attrition rate: 28%	HAD-A	1 (0.41 to 1.59)
					HAD-D	-1 (-1.45 to -0.55)
Armstrong et al 2021 UK (160)	RCT Per Protocol	Stable COPD patients during PR	Pedometer + motivational interview + individual daily step-count target + PR	Usual PR programme delivered as per British Thoracic Society	C-PPAC Total score	8.00 (4.58 to 11.42)
		60 randomised 31 to intervention	Fitburg, Camden, London.		Mean daily steps	1016 (581 to 1451)
					Movement intensity (VMU)	93.00

		29 to control				(44.09 to 141.91)
		8 weeks	Analysed N = 24; Male 9 (37.5%) Mean age ± SD = 71 ± 9	Analysed N = 24; Male 9 (38%) Mean age ± SD = 73 ± 9	Sedentary time (min)	-0.24 (-0.81 to 0.32)
		FEV1% 50.5	Attrition rate: 23%	Attrition rate: 17%	Light time (min)	22.00 (2.56 to 41.44)
					Mod-vigorous time (min)	0.42 (-0.16 to 0.99)
					6WMD (m)	16.00 (-8.12 to 40.12)
					Hand grip strength (Kg)	2.10 (0.62 to 3.58)
					Quadricep capacity (Kg)	0.63 (0.05 to 1.21)
					Sit-to-stand reps (number in 30s)	1.00 (-0.34 to 2.34)
					CAT score	-2.10 (-3.78 to -0.42)
Bently et al 2020 UK(161)	RCT Per Protocol	Stable COPD patients during PR	SMART-COPD intervention consisted of an Android App and wearable activity tracking device with goal setting and feedback	Blinded activity tracker only	Mean daily step count	Lack of data to calculate difference
					Incremental Shuttle walk test	Lack of data to calculate difference
		30 randomised 19 to intervention 11 to control	Fitbit Activity device			
		8 weeks during PR and 8 weeks post	Analysed N = 10; Male 8/19 (42%) Median age (IQR) = 68 (63 – 72)	Analysed N = 6; Male 5/11 (45%) Median age (IQR) = 66 (60 – 70)		
		Not given	Attrition rate: 47%	Attrition rate: 45%		
Benzo et al 2021 USA(162)	RCT Per Protocol	Stable COPD patients	Android tablet with health coaching using video guided exercises, measurement of daily steps and pulse oximetry during exercises	Usual care / Wait list for PR	Mean daily steps	631 (-143 to 1405)
					Sedentary time (min)	-29.90 (-84.70 to 24.90)
		154 randomised 78 to intervention	Vivofit activity monitor (Garmin, Switzerland)		Light intensity time (min)	21.00 (-24.50 to 66.50)

		76 to usual care	Oximeter 3150 Wrist Ox2, Nonin Medical, Minnesota		Mod intensity time (min)	9.70 (-4.25 to 23.65)
					SMAS total score	4.10 (1.68 to 6.52)
		8 weeks	Start study N = 72; Male 34 (47%) Mean age ± SD = 69 ± 8	Study start N = 74; Male 37 (50%) Mean age ± SD = 69 ± 9		
		FEV1% 42.5	Attrition rate: 28%	Attrition rate: 17%		
Cooper et al 2019 USA (189)	OBS	Stable COPD patients	Remote patient monitoring with daily saturations, spirometry, and symptom questionnaires. This was accompanied by an accelerometer worn all the time.	-	Exacerbation detection	Due to poor concordance – unable to calculate
			GeneActiv ® Accelerometer			
		17				
		12 months	N = 17; Male = 5 (29%) Mean age ± SD = 71 ± 7			
		FEV1% 56.8	Attrition rate: 53%			
Chen et al 2022 Taiwan(163)	RCT Per Protocl	Stable COPD patients	Pedometer with step count target	Weekly counselling where participants were encouraged to be active and walk ≥ 30mins/day	Mean daily step count	2358 (738 to 3978)
		45 randomised 21 to intervention 24 to control	Pedometer (brand not mentioned)		6MWD (m)	-13.13 (-47.52 to 21.26)
					CAT score	-6.35 (-11.27 to -1.43)
		6 weeks	Analysed N = 15; Male 13 (87%) Mean age ± SD = 74 ± 8	Analysed N = 11; Male 9 (82%) Mean age ± SD = 72 ± 11	mMRC score	-0.11 (-0.89 to 0.66)
		FEV1% 52	Attrition rate: 29%	Attrition rate: 54%		
Cruz et al 2014 Portugal (164)	OBS	Stable COPD patients	PR with exercise training, psychoeducation, and feedback on physical activity with a wearable monitor	-	Mean daily step count	220 (-565 to 1005)
					Mod-vigorous time (min)	-5.05 (-14.00 to 3.90)
			GT3X Activity monitor		Light intensity time (min)	-0.08 (-28.33 to 28.17)

		20			Sedentary time (min)	-9.6 (-38.06 to 18.86)
		3 months	Analysed N = 16; Male 11 (69%) Mean age ± SD = 66 ± 11		Standing time (min)	30.06 (5.27 to 54.85)
		FEV1% 70.3	Attrition rate: 20%.		Sitting time (min)	2.13 (-8.43 to 12.69)
De-Blok et al 2006 Netherlands (165)	RCT Per Protocol	Stable COPD patients referred to PR aged 40-80 years	Lifestyle physical activity counselling program with pedometer feedback and goal settings in addition to PR	Usual PR	Mean daily steps	567 (-663 to 1797)
					Chair stand test (n)	1.10 (-1.35 to 3.55)
					Arm curl test (n)	2.50 (-0.93 to 5.93)
		21 randomised 10 to intervention 11 to control	Yamax Digi-Walker SW-200 (Tokyo, Japan)		2-min step test (n)	15.00 (-0.99 to 30.99)
					Total SGRQ	3.30 (-6.38 to 12.98)
		10 weeks	Randomised N = 10; Male 5 (50%) Mean age ± SD = 66 ± 10	Randomised N = 11; Male 4 (36%) Mean age ± SD = 63 ± 12		
		FEV1% 47.5	Attrition rate: 20%	Attrition rate: 27%		
Demeyer et al 2017 European (multi-centre study) **(166)**	RCT Per Protocol	Stable COPD and those who had had an exacerbation Not in PR	Tele-coaching with step counter, direct feedback and smartphone app giving activity goals and feedback	Standard leaflet explaining importance of physical activity with a 5–10-minute session explaining	Mean daily steps	1548 (1012 to 2084)
					Moderate time (min)	0.57 (0.35 to 0.80)
					Walking time (min)	17.00 (9.68 to 24.32)
		343 randomised 171 to intervention 172 to control	Fitbug Air		Movement intensity (m/s^2)	0.09 (0.04 to 0.14)
		3 months	Analysed N = 159; Male 111/171 (65%) Mean age ± SD = 66 ± 8	Analysed N = 159; Male 108/172 (63%) Mean age ± SD = 67 ± 8	6MWD (m)	13.51 (3.55 to 23.47)
					Quadricep strength (Kg)	0.05 (-0.17 to 0.27)
		FEV1% 56	Attrition rate: 7%	Attrition rate: 8%	CAT score	-0.47 (-1.89 to 0.95)

Geidl et al 2021 Germany (167)	RCT Intention -to-treat	COPD patients undergoing inpatient rehabilitation	Pedometer given during 3-weeks inpatient rehabilitation then continued after. Feedback and goal setting	3-weeks inpatient rehabilitation and patient education	Means daily steps	496 (-72 to 1063)
					Moderate time (min)	0.21 (-0.00 to 0.43)
					Sedentary time (min)	-0.02 (-0.23 to 0.20)
		327 randomised 167 to intervention 160 to control	Pedometer, brand not mentioned		SGRQ	2.20 -1.12 to 5.52)
					CAT score	-0.79 (-3.06 to 1.48)
		6 months	N = 167; Male = 115 (69%) Mean age ± SD = 58 ± 6	N = 160; Male = 110 (69%) Mean age ± SD = 58 ± 5		
		FEV1% 53.5	Attrition rate: ?%	Attrition rate: ?%		
Hawthorne et al 2022 UK(190)	OBS	COPD patients post acute exacerbation admission	Equivital LifeMonitor to be worn on discharge for 6 weeks. This monitor continuously records respiratory rate, heart rate, skin temperature and physical activity every 15 seconds	-	Changes in the following measures 3 days prior to an exacerbation (n = 11)	
					Changes in heart rate	Increased by a mean 8.1 ± 0.7 beats per minute
		50 recruited	N = 31 Analysed; Male 16 (52%) Mean age ± SD = 69 ± 8		Changes in Respiratory rate	Increased by a mean 2.0 ± 0.2 breaths/min
		6 weeks	Attrition rate: 38%		Changes in skin temperature	Nil change
		FEV1%: 43.5			Changes in physical activity	Nil change
Hornikx et al 2015 Belgium (168)	RCT Per Protocol	Severe COPD exacerbators post hospital discharge	Pedometer used post discharge to provide real-time feedback on step counts. Physical activity counselling telephone calls three times per week with new goals set based on step-count	Usual care (no rehabilitation or motivational messages). General advice about increased physical activity during inpatient stay	Mean daily steps	-29 (-969 to 911)
					Minutes walked	0.00 (-11.50 to 11.50)
					Movement intensity ((m/s^2) / day)	-0.02 (-0.06 to 0.02)
					Quadricep strength (Kg)	0.28 (-0.48 to 1.05)
		30 randomised 15 to intervention 15 to control	Fitbit Ultra (San Francisco, California)		6MWD (m)	3.00 (-53.13 to 59.13)
					mMRC (median and IQR)	Intervention: 0 (-1 to 0)

						Control: 0 (-1 to 0)
		1 month	Overall demographic N = 15; Male = 8 (53%) Mean age ± SD = 66 ±7 Note only 12 analysed	N = 15; Male 9 (60%) Mean age ± SD = 68 ± 6	CAT score (median and IQR)	Intervention: -3 (-10 to 1) Control: -5 (-7 to 1)
		FEV1% 43	Attrition rate: 20%	Attrition rate: 0%		
Hospes et al 2009 Netherlands **(169)**	RCT Per Protocol	Stable COPD patients (45-75 years)	Exercise counselling group: included motivational interviewing based on pedometer feedback	Usual care only	Mean daily steps	2152 (527 to 3777)
					Leg strength (?units)	1.90 (0.66 to 3.14)
		39 randomised 20 to intervention 19 to control	Pedometer (Digiwalker SW-2000, Yamax, Tokyo, Japan)		Arm strength (?units)	6.30 (4.58 to 8.02)
		12 weeks	Analysed N = 18; Male 10 (55%) Mean age ± SD = 63 ± 8	Analysed N = 17; Male 11 (65%) Mean age ± SD = 61±9	Grip force (?units)	0.20 (-4.67 to 5.07)
					6MWD (m)	12.50 (-10.76 to 35.76)
		FEV1% 64.6	Attrition rate: 10%	Attrition rate: 11%		
					SGRQ	-6.60 (-13.22 to 0.02)
Kato et al 2017 Japan (170)	RCT Per protocol	Stable COPD patients	Pedometer to record their number of steps and self-evaluate the cumulative daily step count. No target number given	Usual care with no diary or pedometer	Knee extension strength (WBI)	0.08 (-0.04 to 0.20)
		26 randomised 12 to intervention 14 to control	Omron HJ-205IT pedoemeter (Omron, Tokyo, Japan)		6MWD (m)	43.30 (-15.50 to 102.10)
					SGRQ	-5.10 (-14.73 to 4.53)
		6months	Analysed 6; Male 5 (83%) Mean age ± SD = 74 ± 5	Analysed 5; Male 5 (100%) Mean age ± SD = 73 ± 5	CAT	-2.80 (-8.22 to 2.62)
		FEV1% Not given	Attrition rate: 50%	Attrition rate: 64%		
Kawagoshi et al 2015	RCT	Stable COPD patients	Pulmonary rehabilitation programme with pedometer feedback and goal setting	Home based pulmonary rehabilitation program with 45min monthly education programme	Time spent walking / day (min)	39.00 (0.72 to 77.28)

Japan (171)	Per Protocol				Time spent standing / day (min)	11.70 (-16.83 to 40.23)
		39 randomised 19 to intervention 20 to control	Pedometer (Kens Liferecorder EX, Nagoya, Japan)		Time spent sitting / day (min	53.20 (-20.93 to 127.33)
		12 months	Analysed N = 12; Male 10 (83%) Mean age ± SD = 74 ± 8	Analysed N = 15; Male 14 (93%) Mean age ± SD = 75 ± 9	Time spent lying down / day (min)	-24.30 (-72.00 to 23.40)
		FEV1% 56.6	Attrition rate: 37%	Attrition rate: 25%	Quadricep strength (Kg)	2.90 (-3.42 to 9.22)
					BODE index	-1.76 (-6.25 to 2.73)
					6MWD (m)	-18.59 (-39.55 to 2.36)
					MRC	-0.20 (-0.50 to 0.10)
Kohlbrenner et al 2020 Switzerland (172)	RCT Per Protocol	Stable COPD patients aged over 40, with FEV1 <50% predicted	Physical activity counselling and pedometer with feedback. Activity diary (step counts, daily activity and goal setting) with monthly calls for 3 months, then unsupported for further 9 months	Usual care with no diary and no pedometer	Mean daily steps	300 (-412 to 1012
					CAT score	0.31 (-3.68 to 4.30)
					1min sit to stand reps	1.50 (-2.02 to 5.02)
		74 randomised 37 to intervention 37 to control	Pedometer (Omron Healthcare Co. Kyoto, Japan)			
		12 months	Randomised N = 37; Male 27 (73%) Mean age ± SD = 67 ± 9	Randomised N = 37; Male 23 (62%) Mean age ± SD = 64 ± 9		
		FEV1% 35	Attrition rate: 22%	Attrition rate: 16%		
Mendoza et al 2015 Chile (173)	RCT Per protocol	Stable COPD patients	Pedometer with feedback and goal setting	General counselling monthly and advised to increased activity and walk 30min/day. Paper diary	Mean daily steps	2942 (1881 to 4002)
					6MWD (m)	13.10 (1.24 to 24.96)
		102 randomised 52 to intervention 50 to control	Pedometer (PD724 Triaxial pedometer, Tanita, Tokyo, Japan)		SGRQ	-5.00 (-9.60 to -0.40)
					CAT	-2.90 (-5.33 to -0.47)
		3 months	Randomised N = 52; Male 29 (56%)			

			Mean age ± SD = 69 ± 10	Randomised N = 50; Male 33 (66%) Mean age ± SD = 68 ± 8	mMRC	0.20 (-0.12 to 0.52)
		FEV1% 66.1%	Attrition rate: 4%	Attrition rate: 6%		
Moy et al 2012 USA (174)	OBS	Stable COPD patients	Every step counts walking program which included a pedometer giving feedback with goal setting and motivational messages	-	Mean daily steps	1263 (-268 to 2794)
					mMRC	-0.24 (-0.85 to 0.37)
		27	Pedometer – Omron HJ-720ITC			
		3 months	Recruited N = 27; Male 27 (100%) Mean age ± SD = 72 ± 8			
		FEV1% 55	Attrition rate: 11%			
Nguyen et al 2009 USA (175)	RCT Intention to treat	Stable COPD patients completed PR	'MOBILE-COAHED' – collaborative monitoring of symptoms and exercise (via pedometer) and ongoing reinforcement feedback with weekly messages	'MOBILE SELF-MONITORED' – Symptom and exercise information (via pedometer) but no feedback and no reinforcement	Mean daily steps	-1626 (-3459 to 207)
					Incremental cycle test (watts)	-6.80 (-22.32 to 8.72)
					6MWD (feet)	-114.00 (-341.52 to 113.52)
		17 randomised 9 to intervention 8 to control	Omron HJ-112 digital pedometer (Omron Healthcare, Bannockburn, IL, USA)	Omron HJ-112 digital pedometer (Omron Healthcare, Bannockburn, IL, USA)	SGRQ	8.90 (0.30 to 17.50)
		6 months FEV1% 40.55	Analysed N = 9; Male 3 (33%) Mean age ± SD = 72 ± 9	Analysed N = 8; Male 3 (38%) Mean age ± SD = 64 ± 12		
			Attrition rate: 0%	Attrition rate: 13%		
Nguyen et al 2019 USA (191)	RCT Intention to Treat	COPD patients needing ED attendance	Physical activity coaching intervention – 'Walk-on!' Collaborative monitoring of physical activity step counts, semiautomated step goals and individualised reinforcement	Standard care with no contact with study team	Self-reported activity	-
					All cause acute care use and death	OR 1.05 (0.82 – 1.35)
		2707 randomised 1358 to intervention 1349 to control	Either Omron HJ329 pedometer or Tractivity accelerometer or Fitbit Alta		Hospitalisations	OR 0.84 (0.65 – 1.10)
					Observation stays	OR 0.92 (0.66 – 1.28)

		12 months	Randomised N = 1358; Male 642 (47%) Mean age ± SD = 72 ± 10	Randomised N = 1349; Male 610 (45%) Mean age ± SD = 72 ± 10	Emergency department visits	OR 1.07 (0.84 – 1.36)
					Death	OR 0.62 (0.35 – 1.11)
					COPD-related acute care use	OR 0.96 (0.68 – 1.35)
		FEV1% 61.2	Attrition rate: 76%	Attrition rate: 3%		
Nolan et al 2017 UK (176)	RCT Per protocol	Stable COPD patients undergoing initial PR assessment	Pedometer plus PR, with individualised daily step-count target and weekly review	Standardised twice-weekly outpatient PR program	Mean daily step count	198 (-657 to 1054)
					Mod-intensity time (min)	-0.16 (-0.53 to 0.21)
		152 randomised 76 to intervention 76 to control	Pedometer – Yamax Digi-walker CW700; Yamax, Bridgnoth, UK		Shuttle walk distance (m)	20.00 (-28.91 to 68.91)
					Chronic resp Questionnaire	-7.00 (-22.92 to 8.92)
		6months	Randomised N = 76; Male 56 (74%) Mean age ± SD = 69 ± 9	Randomised N = 76; Male 54 (71%) Mean age ± SD = 68 ± 8		
		FEV1% 50.5	Attrition rate: 26%	Attrition rate: 25%		
Park et al. 2020 Korea(177)	RCT Intention to treat	Stable COPD patients	Combination of group education sessions, prescribed individualised exercises for each participant, pedometer with step count record and symptom monitoring. Built-in smart phone application	Group education sessions and prescribed individual exercises	Mean daily steps	1189 (90 to 2287)
					6MWD (m)	15.41 (-20.01 to 50.83)
					Mod-intensity activity (%of time)	0.02 (0.01 to 0.03)
		44 randmoised 23 to intervention 21 to control	Pedometer brand not mentioned		Sedentary behaviour (% of time)	-0.04 (-0.07 to -0.01)
					SEMCD	-0.04 (-0.87 to 0.73)
		6 months	Analysed N = 22; Male 19 (86%) Mean age ± SD = 68 ± 10	Analsyed N = 20; Male 14 (70%) Mean age ± SD = 65 ± 11	Exacerbation needing hospitalisation (%)	Intervention: 9.1% Control: 10%

		FEV1% 65	Attrition rate: 4%	Attrition rate: 5%		
Robinson et al 2021 USA(178)	RCT Intention to treat	Stable COPD patients	Pedometer with individualised step count goals + objective walking assessment and feedback + motivational messages + online community	Verbal encouragement to increase physical activity and an educational booklet	Mean daily step count	1312 (192 to 2432)
		153 randomised 75 to intervention 78 to control	Fitbit Zip pedometer		6MWD (m)	-12.27 (-38.93 to 14.39)
					SGRQ score	0.07 (-0.25 to 0.39)
		6 months	Randomised N = 75; Male 70 (93%) Mean age ± SD = 69 ± 7	Randomised N = 78; Male 72 (92%) Mean age ± SD = 70 ± 7	mMRC score	-0.13 (-0.45 to 0.19)
		FEV1%: 61%	Attrition rate: 20%	Attrition rate: 31%	Acute exacerbation (%)	Intervention: 12% Control 9%
Spielmanns et al 2023 Germany(180)	RCT Intention to treat	Stable COPD patients post PR	Physical exercise training essions via the Kaia COPD App with an activity tracker. The purpose of he app was to individualise strength training and increase daily steps	Activity tracker but no access to COPD App	Median daily step count	Effect size 0.402 (IQR 0.131 to 0.617
		67 randomised 33 to intervention 34 to control	Activity tracker: Polar A370® Watch		CAT score	-5.12 (-7.53 to -2.71)
					Sit-to-Stand repetitions	1.04 (-1.49 to 3.51)
		6 months	Randomised N = 33; Male 17 (52%) Mean age ± SD = 66 ± 7	Randomised N = 34; Male 17 (50%) Mean age ± SD = 63 ± 8		
		FEV1% 44	Attrition rate: 9%	Attrition rate: 13%		
Sasaki et al 2021 Japan **(179)**	OBS	Stable COPD patients	Pedometer provided. For 8 weeks patients were asked to increase their step count as much as possible using the pedometer.	-	Mean daily step count	205 (-123 to 534)
		19	Pedometer: OMRON healthcare, Kyoto, Japan			

		8 weeks	Analysed N = 16; Male 13 (81%) Mean age ± SD = 73 ± 7			
		FEV1% 56	Attrition rate: 16%			
Valeiro et al 2022 Spain(181)	RCT Per Protocol	Following an acute exacerbation of COPD	Motivational interview with a personalised physical activity program with a pedometer and weekly telephone calls	Usual Care	Mean daily step count	2193 (595 to 3791)
		46 randomised 22 to intervention 24 to control	Pedometer brand not mentioned		Sedentary time (hours)	-0.10 (-1.16 to 0.96)
					Light-intensity time (min)	-16.00 (-32.73 tp 0.73)
		12 weeks	Analysed N = 20; Male 16 (80%) Mean age ± SD = 66 ± 10	Analysed N = 23; Male 16 (70%) Mean age ± SD = 66 ± 10	Mod-intensity time (min)	14.00 (-4.77 to 32.77)
					Quadricep strength (Kg)	1.00 (-2.27 to 4.27)
		FEV1% 46	Attrition rate: 10%	Attrition rate: 4%	6MWD (m)	29.00 (-16.36 to 74.36)
					CAT score	-3.00 (-5.77 to -0.23)
Varas et al 2018 Spain (182)	RCT Per protocol	Stable COPD patients with low physical activity level and no PR for 12 months	5-group sessions of physiotherapy + 8-week community program with exercise training + pedometer with daily step-target. Post intervention – asked to keep same step-count	5-group sessions of physiotherapy. Given a pedometer but no target or instructions	Mean daily step count	2547 (927 to 4167)
					Shuttle test time (min)	7.50 (4.32 to 10.68)
					Shuttle test distance (m)	624.40 (230.76 to 1018.04)
		40 randomised 21 to intervention 19 to control	OMRON walking style X Pocket HJ-320e, Omron Healthcare Inc, Illinois		SGRQ	-5.50 (-8.20 to -2.80)
					mMRC	-0.30 (-0.65 to 0.05)
		12 months	Randomised N = 21; Male 18 (86%) Mean age ± SD = 70 ± 7	Randomised N = 19; Make 13 (68%) Mean age ± SD = 65 ± 9		
		FEV1% 49	Attrition rate: 19%	Attrition rate: 16%		

Vorrink et al 2016 Netherlands (183)	RCT Per protocol	Stable COPD patients	Patients wore a smartphone continuously on a belt which measured physical activity and set individual personalised goals set.	Usual Care	Mean daily step count	-77 (-763 to 609)
		183 randomised 102 to intervention 81 to control	Smartphone – HTC Desire A8181; HTC; Taoyuan, Taiwan		Metabolic equivalent of task	0.05 (-0.10 to 0.20)
					6MWD (m)	-3.20 (-14.51 to 8.11)
		12months	Completed baseline investigations N = 84; Male 42 (50%) Mean age ± SD = 62 ± 9	Completed baseline investigation N = 73; Male 36 (49%) Mean age ± SD = 63 ± 8	BMI (kg.m^2)	0.04 (-0.29 to 0.37)
		FEV1% 56	Attrition rate: 39%	Attrition rate: 27%		
Wan et al 2017 USA (184)	RCT Per protocol	Stable COPD patients	Pedometer and website where step counts uploaded weekly and individualised goal set with iterative step-count feedback and motivational content	Pedometer alone with no website and no step-count goals	Mean daily step count	804 (105 to 1503)
					6MWD (m)	3.50 (-15.92 to 22.92)
					SGRQ	-0.23 (-4.53 to 4.07)
					mMRC	-0.20 (-0.60 to 0.20)
		114 randomised 60 to intervention 54 to control	Omron HJ-720 ITC pedometer			
		3 months	Analysed N = 57; Male 56 (98%) Mean age ± SD = 68 ± 9	Analysed N = 52; Male 51 (98%) Mean age ± SD = 68 ± 8		
		FEV1% 62.6	Attrition rate: 5%	Attrition rate: 4%		
Wan et al 2020 USA* (192)	RCT 2° Analysis	Stable COPD patients 15 months (12 months post study completion)	Secondary analysis of Wan et al 2017 dataset	Secondary analysis of Wan et al 2017 dataset	Risk of acute exacerbations	Rate ratio 0.51 (0.31 to 0.85)
Widyastuti et al 2018 Indonesia	RCT Per Protocol	Stable COPD	Fast-walking at least 30minutes/day and pedometer for 6 weeks with goal setting and feedback	3x30min weekly sessions for 6 weeks of supervised exercise training on a treadmill.	Mean daily step count	264 (-823 to 1351)
					6MWD (m)	-20.80 (-48.89 to 7.29)

(185)				Encouraged to be more active at home with 30min fast walking/day. No pedometer	CAT score	1.20 (-0.51 to 2.91)
		40 randomised 20 to intervention 20 to control	Omron HJ 321, Omron Healthcare CoLtd, Kyoto, Japan			
		6 weeks	Analysed N = 18; Male 16 (89%) Mean age ± SD = 68 ± 7	Analysed N = 18; Male 15 (83%) Mean age ± SD = 69 ± 9		
		FEV1% exact value not given	Attrition rate: 10%	Attrition rate: 10%		
Wootton et al 2017 Australia (187)	RCT Intention to Treat	Stable COPD patients	Unsupervised maintenance walking exercise 3 days a week for 12 months. Telephone calls with biofeedback from a pedometer and progressive goal setting	Unsupervised maintenance walking exercise 3 days a week for 12 months	6MWD (m)	16.00 (-10.20 to 42.20)
					Endurance shuttle walk test time (s)	58.00 (-119.21 to 235.21)
		95 randomised 49 to intervention 46 to control	G-Sensor accelerometer, Pedometers Australia, Cannington, Australia		Incremental shuttle walk test distance (m)	-29.00 (-62.81 to 4.81)
					SGRQ	-3.00 (-7.20 to 1.20)
		12 months	Randomised N = 49; Male 25 (51%) Mean age ± SD = 70 ± 7	Randomised N = 46; Male 30 (65%) Mean age ± SD = 69 ± 9		
		FEV1% 43	Attrition rate: 18%	Attrition rate: 24%		
Wootton et al 2019 Australia (186)	RCT Per protocol	Stable COPD patients	Unsupervised maintenance walking exercise 3 days a week for 12 months. Telephone calls with biofeedback via a pedometer and progressive goal setting.	Unsupervised maintenance walking exercise 3 days a week for 12 months	Mean daily step count	894 (74 to 1714)
					Total energy expenditure (kcal)	5.00 (-106.11 to 116.11)
		86 randomised 42 to intervention 44 to control	G-Sensor accelerometer, Pedometers Australia, Cannington, WA, Australia		Sedentary time (min)	4.00 (-30.60 to 38.60)
		12 months	Randomised N = 42; Male 30 (71%) Mean age ± SD = 70 ± 7	Randomised N = 44; Male 23 (52%) Mean age ± SD = 69 ± 9	Light intensity (min)	24.00 (-12.59 to 60.59)
		FEV1% 44	Attrition rate: 45%	Attrition rate: 55%	Moderate intensity (min)	-10.00 (-25.97 to 5.97)

					Vigorous intensity (min)	0.00 (-1.33 to 1.33)
Wu et al 2021 Taiwan (193)	OBS	Stable COPD patients 67	Prediction system which was made of 4 components: 1. Wearable device (Fitbit Versa) 2. Home air quality sensing device (EDIMAX Airbox) 3. Lifestyle observation platform 4. Health application	-	7-day prediction system for early detection of COPD exacerbations	Accuracy 92.1% Sensitivity of 94% Specificity 90.4% AUROC >0.9
		Exact value not given	N = 67; Male 59 (88%) Mean age ± SD = 67 ± 11			

Abbreviations: 6MWD = Six-minute walk distance; BODE index = body mass index, airflow obstruction, dyspnoea and exercise capacity; BMI = body mass index; CAT = COPD Assessment Tool; CPPAC = Clinical visit-PROactive physical activity in COPD instrument; HAD = hospital anxiety and depression scale; mMRC = modified medical research council; OBS = Observational study; PR = pulmonary rehabilitation; RCT = randomised controlled trial; SMAS = self-management ability scale; SEMCD = self-efficacy for managing chronic diseases SGRQ = St George's Respiratory Questionnaire; WBI = weight bearing index.

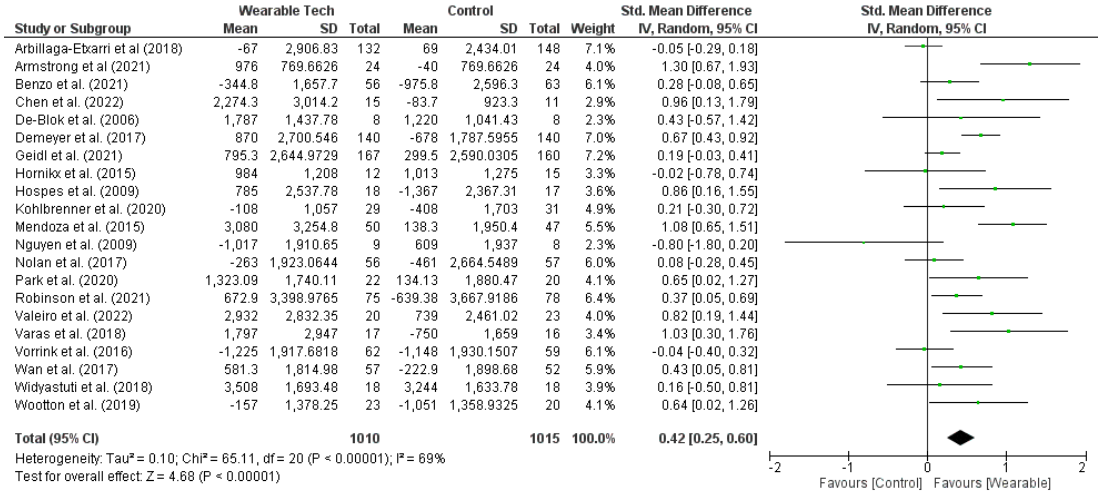
*secondary analysis papers.

2.4.2 Wearable technology and physical activity metrics

Mean daily step count change.

A total of 21 RCTs enrolling 2025 patients with a median (IQR) duration of 3 months (2.3 - 6months), assessed the impact of wearable technology on the mean daily step count. (159, 160, 162, 163, 165-169, 172, 173, 175-178, 181-186) The studies were heterogenous in nature (I^2 = 69%). A random effects meta-analysis showed that wearable technology significantly increased the mean daily step count from baseline, compared to controls [SMD (95%CI) 0.42 (0.25– 0.60)] equating to an improvement of 850 (494 – 1205) steps/day. This is illustrated in Figure 2-2.

Figure 2-2 Forrest plot showing the mean daily step count change.



Subgroup analyses investigating the impact of study duration, type of intervention (wearable technology alone vs. wearable technology combined with additional health coaching vs. wearable technology plus pulmonary rehabilitation), outcome measurement device and COPD severity can be seen in Table 2-2. Wearables combined with another facet (health coaching or pulmonary rehabilitation) had a higher mean difference compared to wearable

technology alone. As expected, studies of a shorter duration also had a higher overall mean difference.

Table 2-2 Subgroup analysis on mean daily steps of included studies.

Subgroups	N	Effect Size Mean difference (95%CI)	I^2 (%)
Duration			
≤ 3months	11	1190 (715 - 1664)	67
> 3months	10	469 (34 – 905)	60
Type of intervention[a]			
Wearable technology[b] with feedback ± goal setting vs. usual care	2	243 (-341 – 801)	37
Wearable technology + health coaching[c] vs. usual care	9	998 (539 – 1456)	55
Wearable technology + pulmonary rehabilitation vs. usual care	3	723 (191 – 1255)	33
Outcome measurement device			
Pedometer	9	1582 (910 – 2255)	64
Accelerometer	10	490 (114 – 866)	77
Severity of COPD			
Moderate	12	1011 (539 – 1482)	78
Severe	8	649 (42 – 1255)	61

[a]This analysis excluded studies whereby the control arm was given a pedometer. It also excluded studies where the control arm had some counselling sessions or encouragement were excluded from this analysis.
[b]all included studies used a step-counter as their intervention.
[c]Health coaching is used to describe motivational interviewing ± counselling ± smart-phone access.

Three observational studies enrolling 66 patients also looked at the impact of wearable technology and changes observed in mean daily step count. None of these studies found a significant difference in the step count from baseline. (164, 174, 179)

Multivariable meta-regression analysis with year of publication, participant age, baseline FEV1 (%predicted), type of pedometer used in the intervention, and outcome measurement device explained 21% of the heterogeneity but was non-significant (residual I2 = 57%, R2 = 21%, p=0.61). The full model results can be seen in Table 2-3.

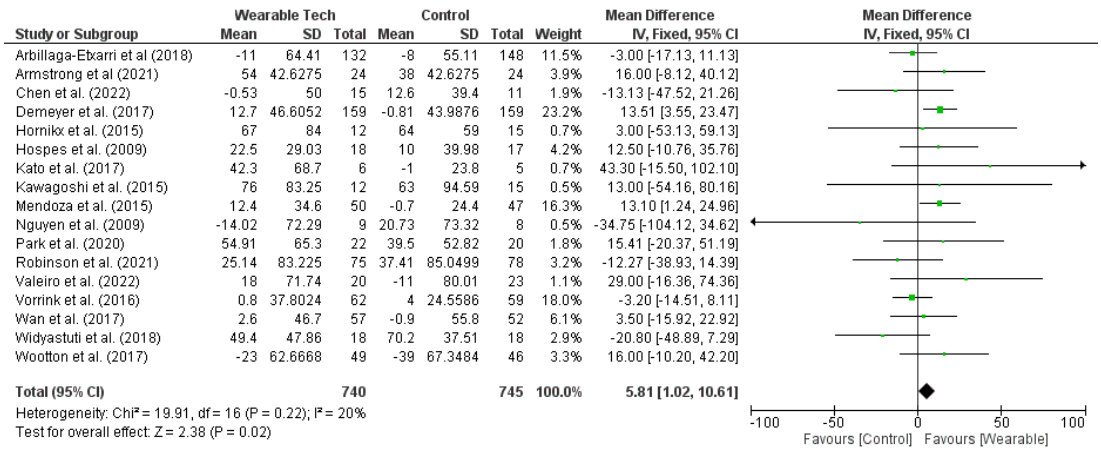
Table 2-3 Multivariable meta-regression analysis results for mean daily step count.

Covariate	Regression Coefficient	P-value	95% confidence interval
Age	-0.1498	0.40	-1.55 to 1.25
Publication year	0.2388	0.15	-0.99 to 1.47
FEV1 (% predicted)	-0.0465	0.40	-1.55 to 1.25
Type of pedometer used for the intervention			
Fitbit Zip	-0.2028	0.89	-14.63 to 14.23
Fitburg	0.4719	0.74	-13.09 to 14.03
G-Sensor	2.0192	0.31	-11.47 to 15.51
Omron	0.2123	0.80	-8.01 to 8.44
PD724	2.0231	0.37	-14.92 to 18.97
Vivofit Activity Monitor	-0.6227	0.73	-18.09 to 16.85
Digi-walker	2.2117	0.30	-12.23 to 16.65
Outcome measurement device			
Dynaport accelerometer	-0.3726	0.74	-11.36 to 10.61
Omron pedometer	0.2930	0.81	-11.83 to 12.42
SenseWear Accelerometer	-2.2625	0.29	-16.13 to 11.61

Six-minute walk distance (6MWD)

A total of 17 RCTs enrolling 1485 participants looked at the impact of wearable devices on the 6MWD.(159, 160, 163, 166, 168-171, 173, 175, 177, 178, 181, 183-185, 187) Studies were not heterogeneous (I^2 = 20%). A fixed-effects meta-analysis showed that wearable technology significantly increased the 6MWD from baseline compared to the control group with a mean difference (MD) (95%CI) of 5.81m (1.02 – 10.61m). Figure 2-3 shows the pooled effect size.

Figure 2-3 Forrest plot showing the six-minute walk distance change.



Subgroup analyses using the same criteria as above can be seen in Table 2-4 and showed that studies which were multi-component and shorter (≤ 3month) had a higher mean difference.

Table 2-4 Subgroup analysis on six-minute walk distance of included studies.

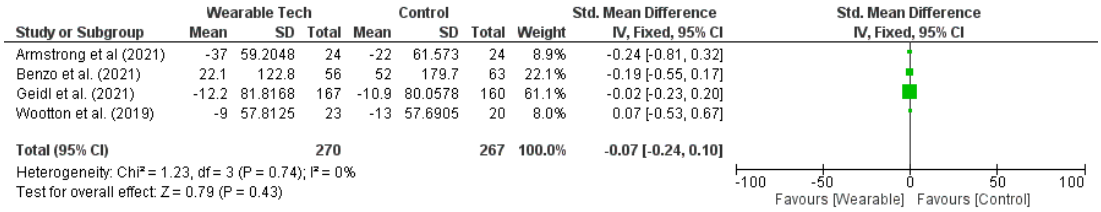
Subgroups	N	Effect Size Mean difference (95%CI)	I^2 (%)
Duration			
≤ 3months	9	10.13 (3.97 – 16.30)	6
> 3months	8	-0.80 (-8.43 – 6.82)	0
Type of intervention[a]			
Wearable technology[b] with feedback ± goal setting vs. usual care	2	-1.54 (-12.64 – 9.56)	57
Wearable technology + health coaching[c] vs. usual care	7	11.75 (3.93 – 19.56)	0
Wearable technology + pulmonary rehabilitation vs. usual care	2	15.66 (-7.04 – 38.36)	0
Severity of COPD			
Moderate	11	5.97 (0.94 – 11.00)	17
Severe	4	12.61 (-7.52 – 32.74)	0

[a]This analysis excluded studies whereby the control arm was given a pedometer. It also excluded studies where the control arm had some counselling sessions or encouragement were excluded from this analysis.
[b]all included studies used a step-counter as their intervention.
[c]Health coaching is used to describe motivational interviewing ± counselling ± smart-phone access.

Time spent in various activity intensities (sedentary, light, moderate and vigorous)

Four RCTs enrolling 537 participants looked at the impact of wearable devices on sedentary time. (160, 162, 167, 186) Fixed effects meta-analysis showed wearables had no significant impact on sedentary time [SMD (95%CI) -0.07 (-0.24 – 0.10); I^2 = 0%]. Figure 2-4 shows the pooled effect.

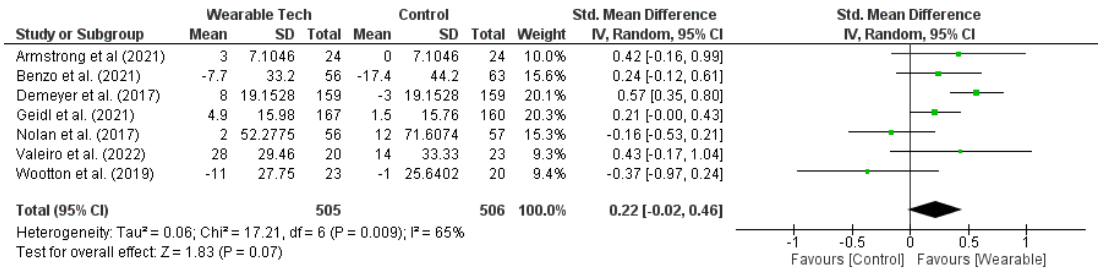
Figure 2-4 Forrest plot showing the time spent sedentary (min)



Two RCTs (160, 186) and one observational study (164) looked at the impact of wearable devices on time spent doing light intensity activities. Armstrong et al (160) found that the intervention group spent longer doing light intensity activities (mean difference 22mins (95%CI 2.56 – 41.44). While Cruz et al and Wootton et al found no difference between the groups. (164, 186)

Seven RCTs enrolling 1010 participants looked at the impact of wearable devices on time spent doing moderate – vigorous activities. (160, 162, 166, 167, 176, 181, 186) Random-effects meta-analysis showed no significant difference between groups [SMD (95%CI) 0.22 (-0.02 – 0.46); I^2 65%). Figure 2-5 shows the pooled effect.

Figure 2-5 Forrest plot showing the time spent in moderate-vigorous activity (min)

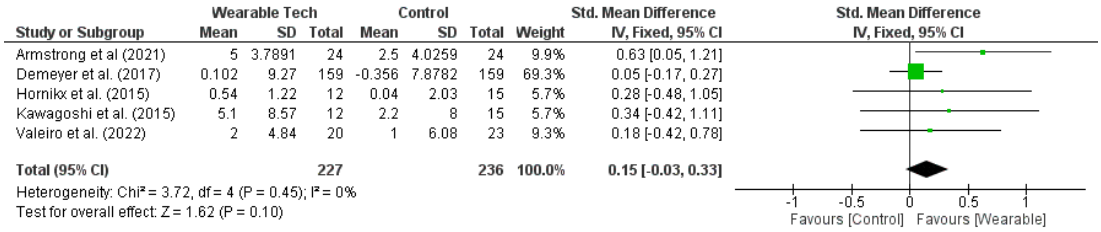


Muscle Strength

Five RCTs enrolling 463 participants looked at the impact of wearable devices on quadriceps muscle strength (Kg). (160, 166, 168, 171, 181) Fixed-effects

meta-analysis showed no significant difference between groups [SMD (95%CI) 0.15 (-0.03 – 0.33); I^2 0%] Figure 2-6 shows the pooled effect.

Figure 2-6 Forrest plot showing quadricep muscle strength.



Two studies investigated hand strength. Armstrong et al (160) found a significant increase in hand grip strength with a mean difference of 2.10Kg (0.62- 3.58Kg) and Hospes et al (169) also found significant increases in arm strength with a mean difference of 6.30 (4.58 – 8.02). The units used in this case were not clear.

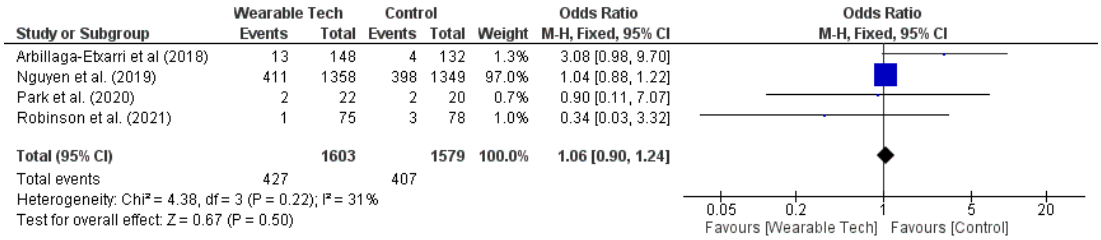
Other activity measures

Other activity measures tested included movement intensity, (160, 166, 168) 1-minute sit to stand repetitions (165, 172) and shuttle walk distance. (161, 176, 182, 187) (Table 2-1) Due to heterogeneity in measurement units and few studies a meta-analysis was not possible.

2.4.3 Wearable technology and exacerbation detection

Ten studies involving 3660 participants investigated the impact of wearable technology on exacerbation detection. (123, 127, 159, 177, 178, 188-192) There was a high attrition rate amongst the intervention groups (median 36% (IQR 9 – 56%). Five studies (159, 177, 178, 191, 192) used physical activity monitors and assessed whether their use was associated with a decreased rate of hospital exacerbations. A fixed effects meta-analysis of four of these studies (median follow up duration 9 months) found no significant difference in the risk of hospitalisation from a COPD exacerbation (pooled OR 1.06 (0.90 – 1.24), I^2 = 31%. (159, 177, 178, 191) This meta-analysis was dominated by the study by Nguyen et al who had a high attrition rate in the intervention group of 76%. This is illustrated in Figure 2-7. Wan et al (192) performed some secondary analysis on a prior RCT and found that the use of a pedometer with individualised targeted goals in a group of stable COPD patients significantly decreased the risk of acute exacerbations over 15months (rate ratio 0.51 (0.31 – 0.85). The absolute values were not given in their paper.

Figure 2-7 Forrest plot showing the pooled OR for an exacerbation of COPD requiring hospitalisation.



The remaining five studies investigated the role of wearable technology in exacerbation prediction. Al Rajeh et al (188) found that a continuous oxygen saturation and heart rate composite score had a positive predictive value of 91.7% for exacerbation detection. The same group then performed some

secondary analysis using non-linear analyses methods including sample entropy of oxygen saturation. They found that the sample entropy of oxygen saturation was significantly higher in the exacerbating group compared to a stable control (0.505 ± 0.159 vs. 0.395 ± 0.101, p = 0.029). (123)

Hawthorne et al (190) found significant changes in both heart rate and respiratory rate three days prior to an exacerbation but no changes detected in physical activity or skin temperature. Heart rate increased by a mean (SD) of 8.1 (0.7) beats per minute for 9/11 exacerbations, while respiratory rate increased by a mean (SD) of 2.0 (0.2) breaths per minute in 7/11 exacerbations.

Wu et al (127) conducted a telehealth study incorporating a wearable device alongside a health application and home air quality device. They had data from 67 COPD patients and followed them up for a mean of 4-months. This resulted in the detection of 25 exacerbations episodes, and a 7-day exacerbation prediction model with an AUC of greater than 0.9, accuracy of 92% with a sensitivity of 94% and specificity of 90.4%. The most important variables in their model were daily steps walked, daily distance moved, and number of stairs climbed.

Cooper et al (189) combined a wearable device with daily spirometry to detect an exacerbation. They enrolled 17 participants with moderate-severe COPD and obtained daily symptom scores and activity levels, as well as measuring daily slow and forced spirometry. However, due to poor adherence of the activity monitor, they could not identify activity patters immediately preceding

or post an exacerbation event and so could not use this to predict exacerbations.

2.4.4 The impact of wearable technology on quality-of-life measures

Secondary analysis measures in 24 studies looked at changes in quality of life. (159, 160, 162, 163, 165-178, 180-182, 184, 185, 187) All the studies involved using a wearable physical activity device.

COPD Assessment Tool (CAT)

A total of 11 RCTs involving 1306 participants looked at the impact of wearable devices on the CAT scores over a median (IQR) duration of 3months (2.3 – 6months). (159, 160, 163, 166, 167, 170, 172, 173, 180, 181, 185) Random-effects meta-analysis showed wearables were associated with a significant reduction in the CAT scores compared to controls with a mean difference of -0.99 (-1.59 to -0.40). Figure 2-8 shows the pooled effect.

Subgroup analysis (Table 2-5) showed that the greatest reduction was seen in patients with severe COPD (mean difference -2.96 (-5.78 to -0.14)).

Figure 2-8 Forrest plot for CAT score.

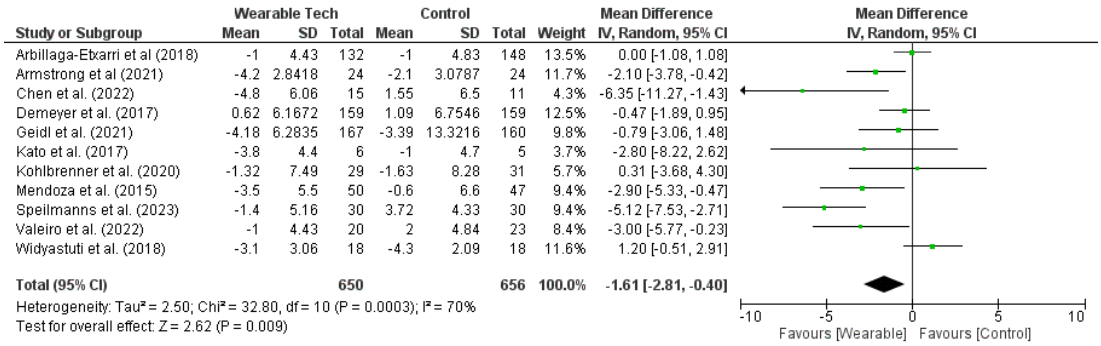


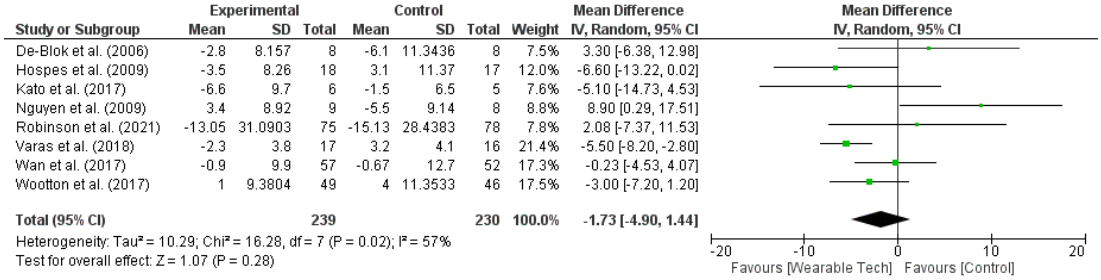
Table 2-5 Subgroup analysis for CAT scores

Subgroups	N	Effect Size Mean difference (95%CI)	I^2 (%)
Duration			
≤ 3months	5	-1.47 (-3.28 - 0·33)	74
> 3months	6	-1.82 (-3.74 - 0·11)	71
Type of intervention[a]			
Wearable technology[b] with feedback ± goal setting vs. usual care	2	-1.09 (-3.19 - -1.01)	0
Wearable technology + health coaching[c] vs. usual care	2	-1.44 (-3.89 – 0.97)	61
Wearable technology + pulmonary rehabilitation vs. usual care	1	-2.10 (-3.78 - -0.42)	-
Severity of COPD			
Moderate	6	-1.35 (-2.56 – 0.14)	59
Severe	3	-2.96 (-5.78 - -0.14)	63

St George's Respiratory Questionnaire (SGRQ)

A total of eight RCTs involving 469 participants looked at the impact of wearable technology on the SGRQ. (165, 169, 170, 175, 178, 182, 184, 187) A random-effects meta-analysis showed no significant difference between groups (MD -1.73 (-4.90 to 1.44), I2 = 57%). Figure 2-9 shows the pooled effect.

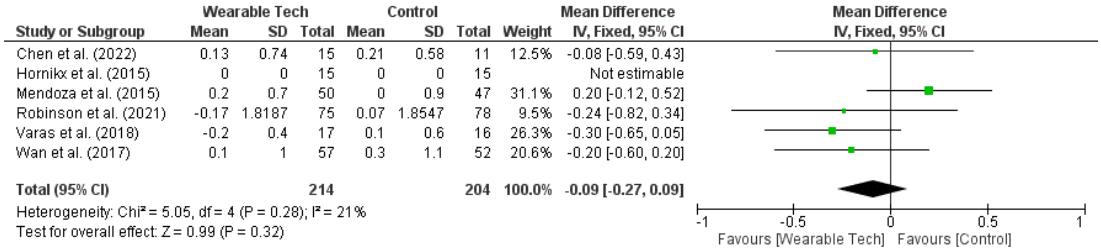
Figure 2-9 Forrest plot for SGRQ score change.



Modified Medical Research Council (mMRC) Score

Five RCTs involving 418 participants investigated the impact of using a wearable device for physical activity on the mMRC score. (163, 173, 178, 182, 184) A fixed-effects meta-analysis found no significant difference between groups (MD -0.10 (-0.30 to 0.11), I^2 = 21%). Figure 2-10 shows the pooled effect.

Figure 2-10 Forrest plot for mMRC score change.



Clinical PROactive physical activity in COPD (C-PPAC) instrument score

Two studies(159, 160) used the C-PPAC score which has previously been validated in COPD patients and requires both questionnaire and accelerometer data. This instrument generates scores of: patients' experiences on the amount of physical activity performed, the difficulty of this activity and a total score. Higher scores indicate a better experience and less difficulty. Meta-analysis showed no significant difference in the score for the amount of physical activity (MD 4.33 (-1.40 to 10.06), I^2 = 69%) but showed a significantly higher score in favour of wearable technology for the difficulty score (MD 5.50 (3.56 to 7.45), I^2 = 22%) and total score (MD 5.74 (1.85 to 9.62), I^2 = 75%). This is illustrated in Figures 2-11, 2-12 and 2-13.

Figure 2-11 Forrest plot for C-PPAC amount score

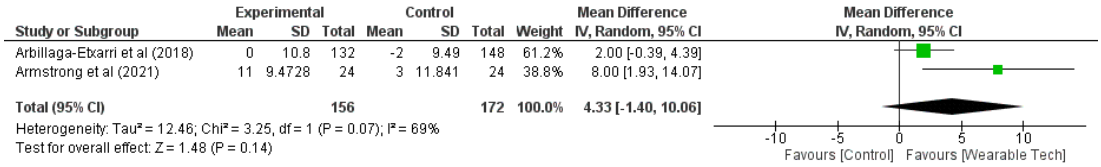


Figure 2-12 Forrest plot for C-PPAC difficulty score

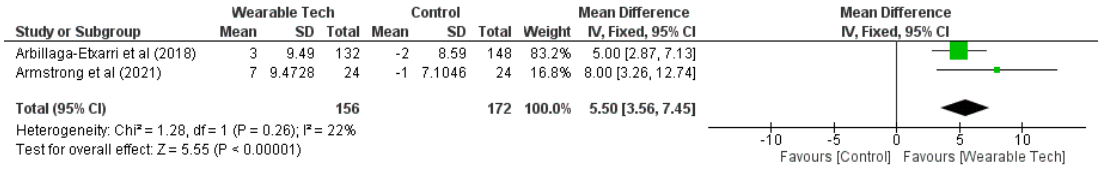
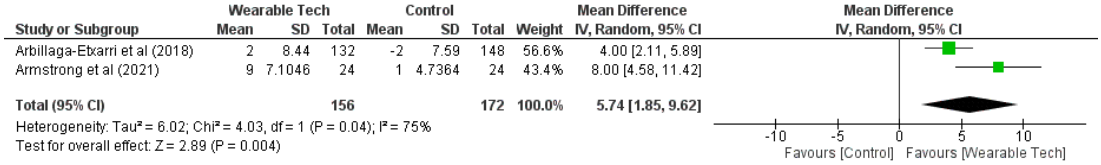


Figure 2-13 Forrest plot for C-PPAC total score



2.4.5 The impact of wearable technology on self-management measures

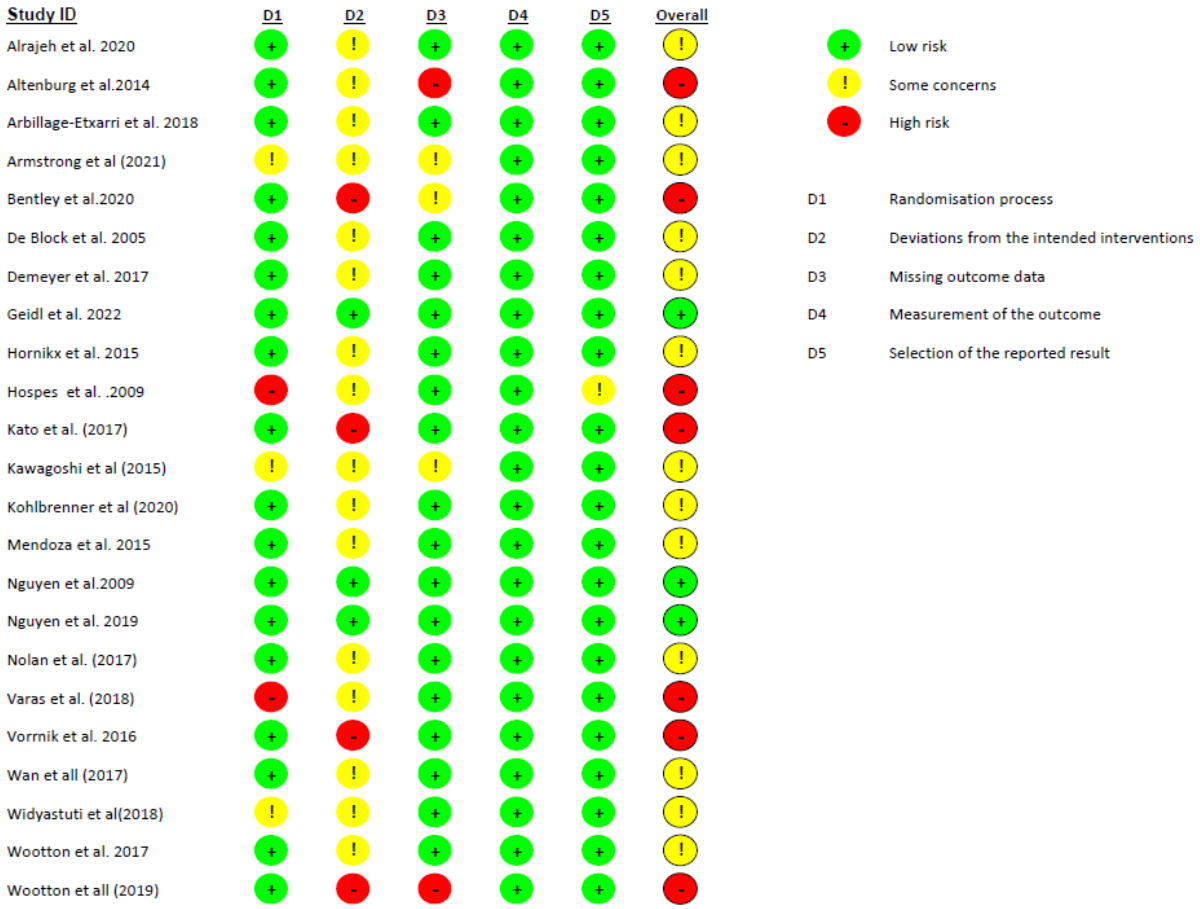
Two studies investigated the role of wearables in COPD self-management through different scoring systems which meant a meta-analysis was not possible. Benzo et al, (162) showed that the wearable intervention significantly increased the self-management ability scale (SMAS) with a mean difference of 4.10 (1.68 – 6.52); while Park et al (177) showed no significant difference when using the self-efficacy for managing chronic diseases (SEMCD) score with a mean difference of -0.04 (-0.84 – 0.73). Both studies used wearable technology with the primary aim of improving physical activity metrics.

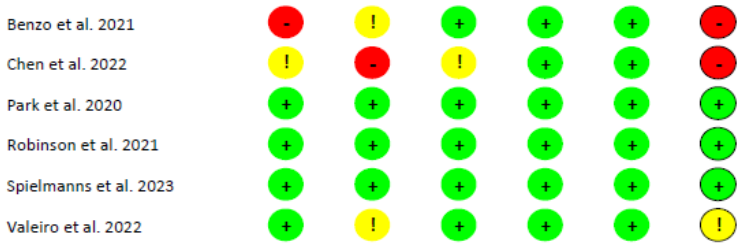
2.4.6 Risk of bias assessment

This review included 30 randomised controlled trials, of which 23 used a per-protocol analysis and seven used an intention-to-treat analysis plan. The quality of these trials was assessed using the Cochrane risk-of-bias tool and the domain ratings and overall ratings can be seen in Figure 2-14. Overall, a large number of studies had concerns in the domain looking at deviations from the intended interventions due to the per-protocol analysis employed, and the high drop-out rate in a large number of studies may have affected the overall results. Studies had a low risk of bias in most of the other domains.

There were seven observational studies. One of these was a secondary analysis of a RCT. The quality of these trials was assessed using the Newcastle Ottawa Scale and the domain and overall ratings can be seen in Table 2-6. A score of ≥ 7points is considered a good rating.

Figure 2-14 Detailed quality assessment for the randomised controlled trials





*Wan et al (2020) not included in this analysis as it was a secondary analysis to a previous RCT.

Table 2-6 Detailed quality assessment of the observational studies

Author, Year	Population representative	Selection of non-exposed cohort	Exposure	A priori Outcome	Comparability	Outcome assessment	Follow-up duration	Follow-up adequacy	Total rating (max 9)
Cooper et al (2019)	1	1	1	1	1	1	1	0	7
Hawthorne et al (2022)	1	1	1	0	1	1	1	1	7
Moy et al (2012)	1	1	1	1	2	1	0	1	8
Rubio et al (2017)	1	1	1	1	2	1	1	1	9
Sasaki et al (2022)	1	1	1	1	2	0	1	1	8
Wu et al (2021)	1	1	1	1	1	1	0	1	7

*Al Rajeh et al (2021) not included in this as it was a secondary analysis and the initial study has been included in the ROB assessment tool in Figure 4-14

2.5 Discussion

This systematic review and meta-analysis, has shown: 1) home wearable technology significantly improved the mean daily step count in COPD patients over a median duration of 3 months, with an average effect size of 0.42, equating to a clinically important difference of 850 (494-1205) steps [minimal important difference (MID) 600-1100 steps/day (194)]; 2) wearable technology significantly increased the 6MWD with a mean difference of 5.81m (1.02 – 10.61m), however, this was below the MID of 25m (195); 3) wearable technology significantly decreased the CAT score (MD -0.99 (-1.59 to -0.40)) but this did not reach the MID of -2 points; (196) 4) wearable technology may support COPD exacerbation detection, however, studies were heterogenous with mixed outcomes and had a high attrition rate, suggesting further work in this field is necessary to draw firm conclusions; 5) wearable technology had no significant impact on other activity or quality of life metrics.

2.5.1 Physical activity outcome measures

To my knowledge this is the largest systematic review and meta-analysis to date, investigating the role of wearable devices in improving physical activity outcomes in a COPD population. The increase in mean daily step count is within the previously reported MID range and is higher than 600 steps/day, which has previously been shown to reduce the risk of hospitalisation. (194) Furthermore, wearable technology is likely to have a greater positive impact on physical activity and step-count than exercise training programs alone, long-term oxygen therapy of neuromuscular stimulation. (197, 198) However, it is worth noting that the studies in this meta-analysis were heterogenous, likely due to different intervention designs and devices. This heterogeneity

could not be explained by the multivariable meta-regression analysis, suggesting a degree of caution is needed in interpreting these findings. The year of publication also had no effect and so this heterogeneity is unlikely due to improvement / ease of technology.

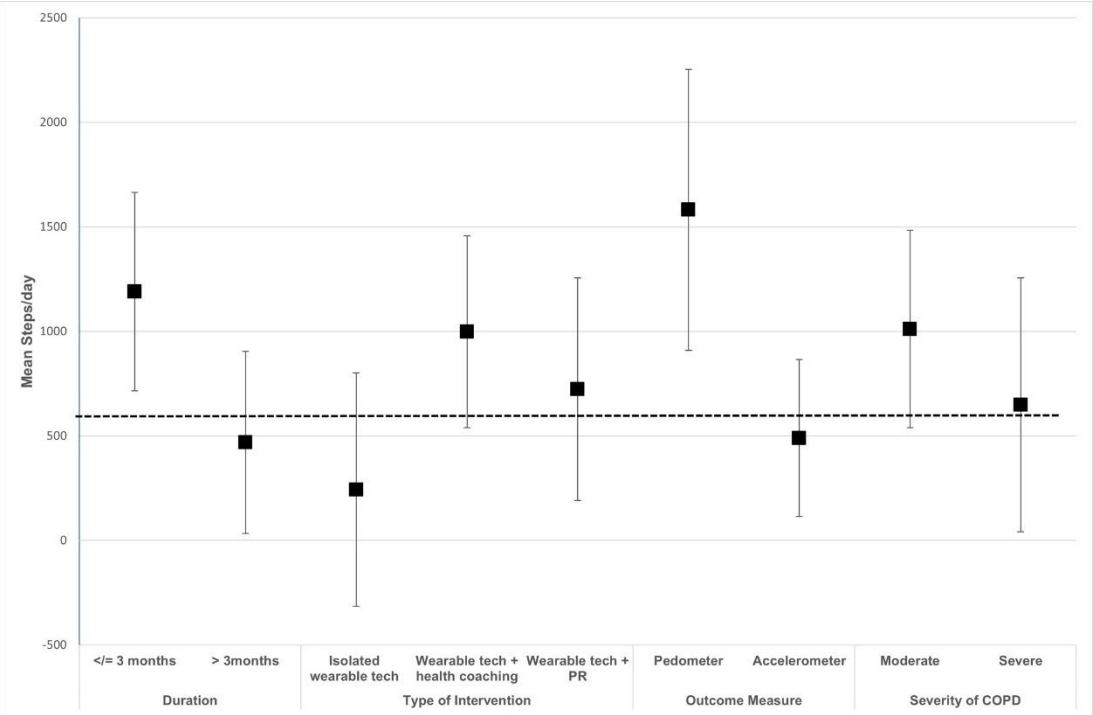
While my findings echo previous reviews, which have also showed that step-counters improve mean daily step count, (113, 149-151) key points of difference lie in our sub-group analyses which were not performed by the other studies. First, isolated pedometer use (with feedback and goal setting) showed no significant difference when compared to usual care (MD 243 (-314 – 801steps/day). Second, it is apparent that wearable technology coupled with another intervention, such as health coaching (e.g., motivational interviewing and counselling) or pulmonary rehabilitation significantly improves the mean daily step count. This suggests that wearable technology interventions which are muti-faceted are more effective in improving physical activity. This is illustrated in Figure 2-15.

Subgroup analyses also found that the increase in mean daily step count was lower in studies of longer duration (>3months). This is illustrated in Figure 2-15. However, it is worth noting that studies using wearable technology for a longer duration (>3months) had a higher drop-out rate (23% vs. 15%), and most of these studies used a per-protocol analysis, meaning they will be subject to attrition bias. It may also suggest patients find it difficult to use pedometers over a longer-term period, and perhaps, other forms of more acceptable wearable devices are needed to realise longer term benefits. It is possible that during this time participants had disease progression or had more time for other influences, such as exacerbations, meaning they dropped out of

the study. The initial novelty of using a wearable may also wear off. Further work in this field is necessary to understand the true long-term impact of wearables on physical activity.

We also found that the device used for measuring the outcome of interest (pedometer vs. accelerometer) significantly impacted the overall result. (Figure 2-15). This may be due to accelerometers being a validated tool to measure step count in COPD patients, meaning that pedometers may over-estimate the true effect. (199) While the data from Armstong et al (149) agrees with this finding, that from Qui et al are contrary. (113) Given the indirect comparison made in this meta-analysis, future confirmation may be required through a one versus one design.

Figure 2-15 Subgroup analyses of the differences in daily steps achieved according to the MID



The dotted line represents a mean daily step count of 600 steps/day (MID)

Unsurprisingly, patients with severe COPD had decreased improvement in their daily steps compared to moderate COPD patients, likely due to decreased exercise capacity and reserve. Although it is worth noting that patients with severe COPD make the best gains with pulmonary rehabilitation and analysing further sub-groups (e.g., the type of intervention and severity) may lead to different results.

Our meta-analysis showed that wearable technology was associated with an improvement in the 6MWD by 5.81m (1.02 – 10.61m). This is similar to previously published data by Qui et al, who found a change of 11.6m. Both these values fall short of the previously published MID of 25m, (195) but are higher than the change associated with telehealth interventions (1.3m). (200)

It is worth noting that a previous study has shown that even a 6m increase in the 6MWD is associated with an approximately 4% risk reduction in all-cause and respiratory mortality on COPD patients. (201) Once again, it seemed that studies with shorter durations had a greater improvement in the 6MWD compared to studies of >3month duration. Studies of longer duration had a greater drop-out rate, meaning more attrition bias which could explain the results somewhat. This could also imply that participants found it difficult to use pedometers for a longer duration. Therefore, future work is needed to ascertain whether the short-term gains achieved by wearables translate in the longer term.

Our systematic review has shown for the first time, that wearable technology is not associated with different times spent at different activity intensities or quadriceps strength. This is not unsurprising as most studies utilised pedometers, which primarily act to count and feedback steps. They do not direct the speed of the steps, nor are they strength training devices. A recent review by Cochrane also found minimal improvements in physical activity intensity with pulmonary rehabilitation, even when additional measures such as inspiratory muscle training and physical activity counselling were added. (202) Future studies need to focus on wearables specifically designed to improve physical activity intensity in patients with both stable COPD and in patients immediately post exacerbation, given this is a high risk group, (203) to realise short and long-term benefits in this population. This is vital, as prior work has shown that a minimal increase in activity intensity level reduces the risk of COPD admissions and all-cause mortality. (109)

Therefore, while wearable technology has been shown to improve the mean daily step count and 6WMD in the short term, benefits with regards to physical activity intensity and muscle strength are yet to be seen. The longer-term benefits of wearable technology to improve physical activity needs to be fully investigated in well powered studies. This is vital to ensure persistent gain in this patient population.

2.5.2 Exacerbation detection

Exacerbation detection and early treatment is of vital importance in COPD management, as it has been established to be the most important predictor for future exacerbations and deteriorations. (36) To my knowledge, this is the first systematic review to explore the role of continuous wearable technology monitoring in aiding exacerbation detection. While a prior review investigated the role of monitoring physiological parameters, all the studies included in that review used intermittent monitoring. (204)

In this review, five studies (159, 177, 178, 191, 192) examined the association between use of physical activity monitors and the rate of exacerbations. While a meta-analysis of four of these studies found no significant difference (OR 1.06 (0.90 – 1.24), this was dominated by one large study (n = 2707) (191) and so needs to be interpreted with caution. Furthermore, the primary aim of these studies was to improve physical activity, rather than use wearables to support exacerbation detection, which was not the primary outcome for these studies.

Three studies used composite scores combining several measures to predict exacerbation onset. While one study combined a wearable device with daily

spirometry, poor concordance meant no analysis could be performed. (189) Both the remaining studies suggested high positive predictive values in exacerbation prediction of over 90%. While this is encouraging, some caution must be exercised. Al-Rajeh et al (188) had a high attrition rate of 52% and only included 13 patients in the final analysis, resulting in low total numbers and a study that was underpowered for exacerbation; and Wu et al (193) used a prediction system combining several factors including environmental measures which can be very costly and cumbersome to replicate in the non-research setting. Moreover, their study also included only 25 acute exacerbation events, meaning more data in this field is necessary.

While the data so far, has mixed outcomes, it does seem to suggest that continuous monitoring of physiological parameters may hold the key to detect exacerbations early. Future work needs to focus on using wearables to identify differences between stable and exacerbating patients, such that algorithms can be developed to detect change and institute management early. It is also important that these wearables are simple to use and acceptable to patients.

2.5.3 Quality of life measures

To my knowledge this this first review looking at the impact wearable devices have on validated quality of life measures. Over a median duration of 3 months, wearables were associated with a significant reduction in the CAT score by -0.99 points, below the MID of -2 points(196) and thus unlikely to be clinically relevant. Although, it is worth noting that a certain proportion of participants in these trials will have achieved the MID and whilst no study performed responder analysis, a dedicated study investigating the association of wearable technology and CAT score may be useful. Moreover, subgroup

analysis showed that patients with severe COPD seemed to have a greater reduction in their CAT score (-2.96 (-5.78 to -0.14)). This is relevant, as this patient population often have a high disease burden and therefore reducing their CAT score may have a large improvement in their quality of life.

We found no evidence that wearable devices improved the SGRQ score or mMRC score. Quality of life measures were secondary outcomes in all the studies. While these studies showed an increased mean daily step count, there was no change in the time spent in various activity intensities. This may account for a lack of improvement in quality-of-life measures as previous work has shown that higher levels of moderate intensive physical activity is associated with improved health related quality of life. (205)

Similar findings have also been found in a recent umbrella review of five systematic reviews looking at the impact of activity trackers on psychosocial outcomes and quality of life in healthy participants. These results may be because quality of life measures rarely consider participants' perspectives or views of the actual activity. Two studies (159, 160) in this review, incorporated the C-PPAC instrument (206) which assesses patients' experience of the amount of physical activity and difficulty experienced with the actual activity. Meta-analysis of these two studies suggested that wearables improved both the difficulty score (i.e., patients had less difficulty with physical activity at the end of the intervention) and total score. The difficulty dimension of the tool has a moderate-strong correlation with health status, chronic dyspnoea, and exercise capacity. (206) While these results are encouraging, they need to be interpreted with some caution given only two studies have used this instrument.

Overall, it is probable that quality of life is a key motivator for physical activity. Therefore, if wearables of the future can improve both quality of life while improving physical activity, it is more likely that patients will continue to use the devices and gain benefit in the longer term.

2.5.4 Self-management

Only two studies looked at the association of wearables and improvement in COPD self-management using different scoring systems. The studies showed contrasting outcomes with Benzo et al (162), showing significant increases in the SMAS score and Park et al (177) showing no change in the SEMCD score. Further work in this field is necessary to ascertain whether wearables have a role in improving the self-management in COPD patients.

2.5.5 Quality of the evidence

The overall quality of evidence from the RCTs had some concerns on the Cochrane Risk of Bias Tool, mainly due to the per-protocol analyses employed by most studies and subsequent attrition bias. Studies had a low risk of bias with regards to other criteria including the randomisation process and outcome measurements. The observational studies were of good quality overall with all having a rating of greater than or equal to seven out of nine on the Newcastle Ottawa Scale.

2.5.6 Strengths and limitations

This systematic review and meta-analysis is the largest and most robust review of the use of wearable devices to aid physical activity promotion. We are also the first to report that current wearables have no impact on physical activity intensity levels, muscle strength and a limited impact on quality-of-life

measures and acknowledge that further work delineating the role of wearables for COPD exacerbation detection is needed.

Several limitations should be noted. Firstly, the studies were heterogenous with different patient cohorts and used different objective outcome measures and different wearable devices. This was not significantly accounted for by meta-regression analysis, and therefore direct comparison between studies may be somewhat limited. However, the random-effects model and SMD used in the meta-analysis should reduce bias attributed to this. Secondly, studies using pedometers differed in their approach to setting an individualised step target which means direct comparison between studies will inherently have some bias. Thirdly, wearables were often combined with other health interventions, such as motivational interviewing and walking programs, which means identifying the exact impact of the wearable may be under or over-estimated. Fourth, several studies had a high drop-out rate which was not appropriately accounted for in the analysis. This led to attrition bias in most studies which will invariably impact the outcomes. Finally, despite a comprehensive literature search, there exists the possibility that some eligible studies were missed. Furthermore, restricting the studies to English and not searching for unpublished studies may result in selection and publication bias.

2.5.7 Conclusion

In conclusion, this review and meta-analysis suggests that home wearable devices significantly improve the mean daily step count and physical activity capacity as measured by the 6MWD. However, this increase does not seem to translate to an increase in time spent doing moderate-vigorous activity. Currently wearables have a limited impact on patient quality of life, and the

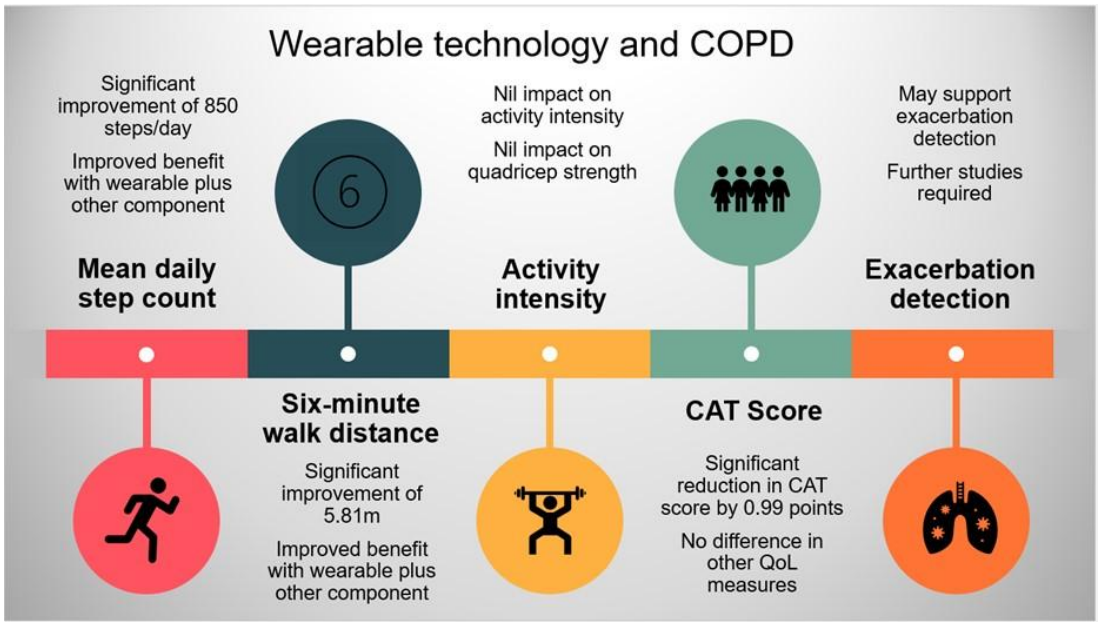
gains seen in physical activity metrics are likely to be short-lived. While there is limited data, wearables are likely to improve the detection of COPD exacerbations, however, further work is needed in this field. The main findings from this review are summarised in Figure 2-16.

Future work needs to focus on how to improve wearable technology longevity. This would be helped by improving patient quality of life alongside improving physical activity metrics. This would translate into longer term gains and help improve patient morbidity and mortality.

Overall, wearables seem to have the potential to become a core part of future COPD management and improve health outcomes, but further work is required for this to become a reality.

Having understood the current landscape of wearable technology in different facets of COPD management, the next chapter explores the acceptability of future wearables in a group of patients with chronic respiratory disease. This is to understand how to ensure future, novel wearables can maximise use and longevity.

Figure 2-16 Summary infographic.



CHAPTER 3

3. Chapter 3: The acceptability of wearable technology for long-term respiratory disease: a cross-sectional survey

3.1 Background

Chronic respiratory disease affects a large number of patients in the UK and is responsible for more than 700,000 hospital admissions and over six-million inpatient bed-stays in the UK each year. The British Lung Foundation (BLF) estimates that about one in five people in the UK suffers with a long-term respiratory condition such as asthma or chronic obstructive lung disease (COPD). This has a significant effect on patient morbidity, mortality and the healthcare economy. (207)

The World Health Organisation (WHO) has recognised a shift in healthcare to one where digital health care, including wearables, are the future. (93) This is perhaps even more important in the current climate given the recent global pandemic, which has seen the rise of remote consultations, coupled with a huge backlog of routine patient appointments. Wearable technology has real potential to change the way patients are managed, reduce hospital admissions and improve the outpatient pathway. It can empower patients to take control of their condition, improving quality of life, reduce disease burden and improving their overall experience of healthcare. However, to maximise their benefit, understanding patient acceptability to wearables is vital.

While there have been several studies looking at the usability of wearables in chronic disease, a recent systematic review concluded that this is often poorly reported and measured. (208) Moreover, usability of a device is often summarised with wear-time and adherence data. (209) This is not the same

as acceptability of the wearable device. Models of acceptability include other factors such as user characteristics, attitudes about technology, product characteristics and social influence. (210-213)

There have been few studies that have investigated the acceptability of wearables in long-term respiratory disease. Prinable et al conducted an online survey (n=134) to assess key device attributes for a wearable that can be used for long-term monitoring of breathing in patients with chronic asthma. They concluded that the majority of patients would be willing to wear a device (62%) and most participants would prefer to use a wrist watch (92.5%).(214) Simmich et al. looked at older patients with COPD and their perspectives of wearable devices. They used semi-structured interviews and concluded that wearables were perceived to be useful to facilitate goal-setting and visualise long-term improvements. (215) Finally Keogh et al. looked at the acceptability of a waist-worn device (McRoberts Dynaport MM+) which measured mobility remotely and included 25 patients with COPD. Semi-structured interviews showed the device was easy to use and comfortable but not considered useful due to the lack of interaction with the participant. (216)

A systematic review in 2021 assessed patients' perceptions and experiences of wearing physical activity monitors (including smartphone apps and wearables) in a COPD population. They included 12 studies (n=424) in their qualitative analysis. They developed seven different themes across the study and concluded that overall people with COPD liked using the technology and found it useful in increasing their physical activity level. The review also highlighted some negative experiences including some frustration with inaccurate monitoring, technical issues, and the time-consuming nature of

monitoring. Feedback from monitors, goal setting and self-monitoring were popular with patients. Overall, the authors felt that there is limited research exploring views of how people with COPD actually integrate technology in their lives and this therefore is something that needs to be explored in the future. (114)

Given the paucity of data in chronic respiratory disease, further work to investigate patient perspectives and acceptability of wearables is necessary. This will enable us to build models for patients with chronic respiratory disease and guide future wearable design, to maximise benefit, and use in the long-term.

3.2 Aims

The primary aim of this cross-sectional survey was to identify the acceptability of wearable technology in a group of patients with chronic respiratory disease.

The secondary aims of the survey were to:

- Identify patient preferences in wearable technology design.
- Identify the impact of social norm perspectives on wearable technology.

This survey, and therefore some of the figures and tables in this chapter, have already been published in *Heliyon* in August 2024 (DOI: 10.1016/j.heliyon.2024.e35474) under the creative commons attribution (CC BY 4.0). (217)

3.3 Methods

3.3.1 Ethical approval

This cross-sectional survey received ethical approval from the Health Research Authority and Care Research Wales (HCRW), REC reference 22/NS/0017.

3.3.2 Survey design

This was a cross-sectional survey to identify various factors that affect patients' acceptability to wearable technology and assess their current use of any wearables. The survey was also designed to identify any patient preferences in wearable design and the impact of social norm perspectives on wearable technology. The survey was designed to be completely anonymous.

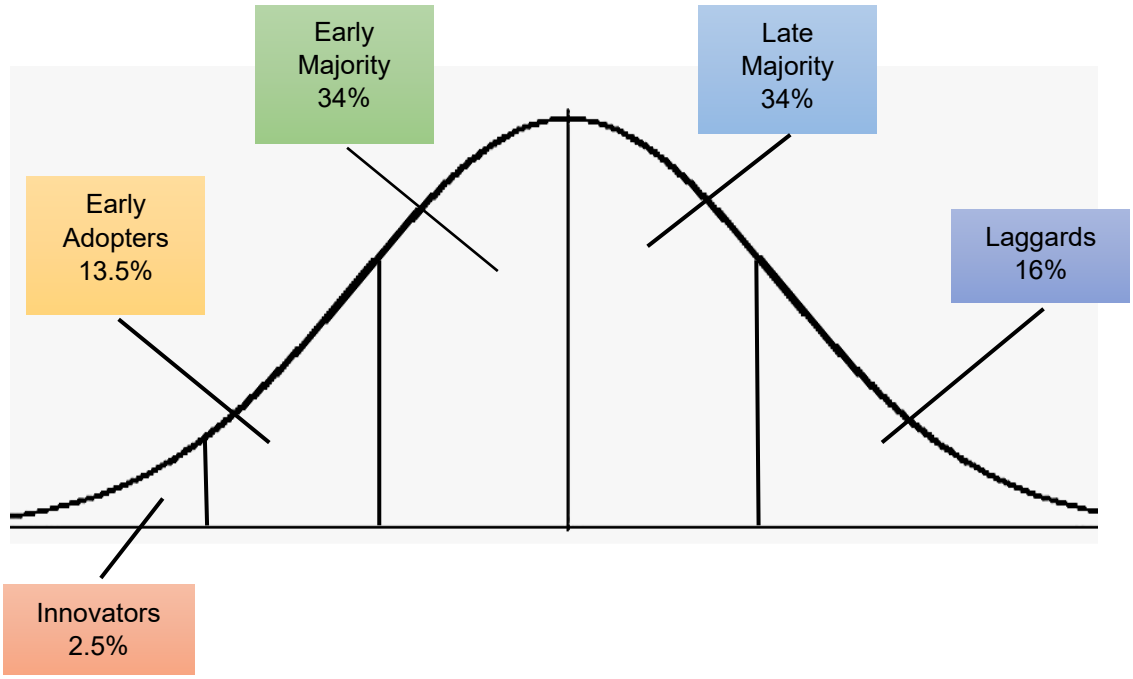
The survey questions were initially designed using four well described models of acceptance of technology, and social behavioural theories:

1. Diffusion of Innovation Theory

Rogers (1983) defines diffusion as 'the process by which an innovation is communicated through certain channels over time among the members of a social system.' (218) He also distinguished five different categories of adopters of an innovation as outlined by the bell-curve in Figure 3-1 (adapted from Peterson and Kaminski) (219, 220)

Figure 3-1 Diffusion of innovation theory bell curve.

(adapted from Peterson and Kaminski) (219, 220)



Innovation ‘diffuses’ through the different categories and as early innovators and adopters ‘spread the word’ more people become open to the idea of the innovation.

Furthermore, various diffusion studies have demonstrated a classic sigmoid (S-shaped curve) of over-time adoption for innovations perceived to be useful.

The key component affecting diffusion are outlined below: (210, 219)

a. The innovation – especially the adopters’ ideas behind its relative advantage, complexity, and ability to fulfil a goal.
b. The Adopter – (based on the adopters’ degree of innovativeness, as demonstrated by the bell-shaped curve)

c. The social system – this includes the potential adopters' perception or ideology of the social pressure to adopt a particular innovation.
d. The individual adoption process which includes:
    i. The awareness of the need for an innovation
    ii. The interest in this new idea and seeking of information about it.
    iii. The decision or evaluation stage (where they weigh up whether or not to try the device).
    iv. The trial stage of the device.
    v. The decision for continued use of the innovation.
e. The diffusion system – for example the role of an external change agency – this is akin in today's work of a social media influencer or 'innovation champion'.

2. The theory of reasoned action (TRA)

The theory of reasoned action (TRA) was first described by Fishbein & Ajzen in 1975. Central to this theory is that the most important determinant of a particular behaviour is the behavioural intention. Determining features of this intension include attitudes towards performing that behaviour and the subjective norms associated with a particular behaviour. Attitudes can be determined by an individual's normal beliefs and their beliefs about the outcomes of a particular behaviour. For example, if someone had strong belief that wearable technology is the future and will have good outcomes in healthcare, they are far more likely to engage with it. Subjective norms are

determined by whether an individual feels certain people (family, friends etc.) would approve of a particular behaviour. (212)

3. The theory of planned behaviour

The theory of planned behaviour (TPB) was developed as an extension to TRA. The TRA assumes that behaviour can always be controlled and is voluntary. However, this may not always be the case. This led to the development of the TPB. In addition to attitudes towards a particular behaviour and subjective norms, TPB introduces the concept of perceived behavioural control. This refers to an individual's perception of how easy or difficult the behaviour in question is. This will of course vary depending on the situation and so leads to differing perceptions that are situation dependent. (221, 222)

4. Technology acceptance model

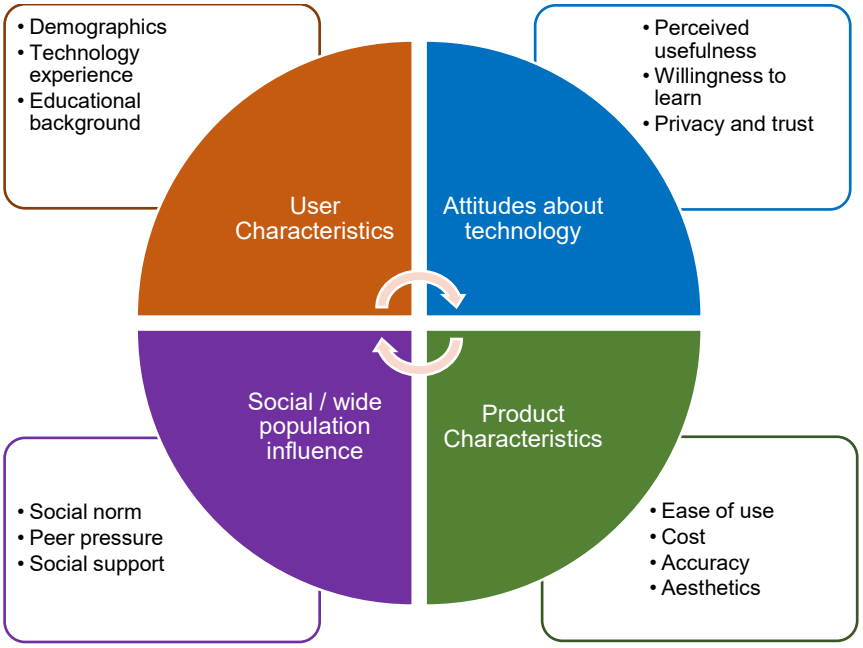
The technology acceptance model (TAM) was introduced by Fred Davis in 1989. The underlying principles of this model are based on two factors which determine whether any computer system (such as wearable technology) will be accepted by users: (211)

i. Perceived usefulness – this can be defined as the degree to which someone believes using a particular system will improve an aspect of their life.
ii. Perceived ease of use – this would equate to the amount of effort someone felt would be needed to use the system.

Overall, four main themes that were universal to all these models were identified. These can be seen in Figure 3-2 below. This was echoed by Sun et

al who conducted a survey on the acceptance of personal health devices amongst all patients with chronic conditions in China. (213)

Figure 3-2 Four common themes of technology acceptance.



A total of 27 questions were initially developed based around these four themes. A draft of the survey was built on SurveyMonkey®. These were then reviewed by an Asthma-UK / British Lung Foundation expert patient panel. This panel kindly reviewed the questions and provided in-depth feedback, both on the layout of the questions on SurveyMonkey® and the actual questions and whether they were appropriate to answer the main research aims. Following this feedback, a finalised survey was developed for use in this study. The final survey had 24 questions which can be seen in the Appendix (Chapter 7.4) Ten questions used a 7-point Likert scale ranging from 1: strongly disagree to 7: strongly agree. Two questions were presented in the reverse order to ensure survey validity. If a respondent gave inconsistent answers in

either reverse question, their answers were eliminated from the valid data set to be analysed.

The finalised survey was sent out to patients via the following different pathways to maximise responses:

1. Respiratory clinics at Royal Free Hospital
2. Respiratory clinics at Barnet Hospital
3. Via the Asthma UK – British Lung Foundation Respiratory Voices Network
4. Via social media

The respiratory clinics at Royal Free Hospital and Barnet Hospital are a mix of general respiratory clinics, specialist asthma, COPD, sleep and ventilation, interstitial lung disease and lung cancer clinics.

Patients had the option of completing the survey online (via SurveyMonkey®) or via a paper version which was then transcribed online. All the survey information was completely anonymous.

3.3.3 Inclusion and Exclusion Criteria

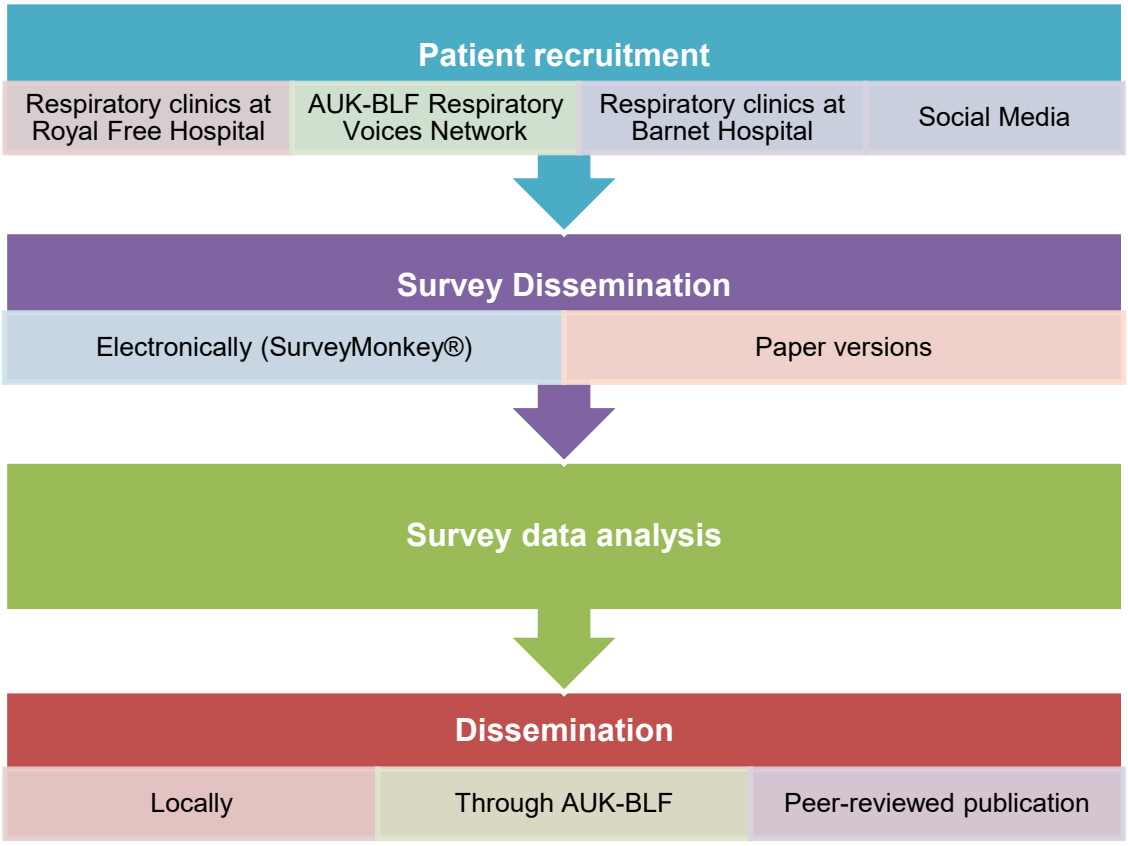
Inclusion Criteria:

- All patients with a diagnosis of chronic respiratory disease

Exclusion Criteria:

- Age < 18years
- Participants not fluent in English
- Participants unable to give consent

3.3.4 Study flow chart



3.3.5 Statistical analysis

The statistical analysis used both quantitative and descriptive methodology. Patient baseline characteristics were summarised in a descriptive manner and tabulated. Any survey responses with a lack of consent or no information were excluded, and any survey responses with inconsistent answers in any of the reverse questions were also excluded. The data was exported to SPSS statistical software for further analysis.

Ten questions had a 7-point Likert scale response, but one of these was dependent on whether participants had already used wearable technology. The internal validity of the remaining nine questions was assessed using Cronbach alpha. I then performed exploratory factor analysis to assess whether common factors emerged from these nine questions. Common factor

analysis with maximum likelihood and direct Oblimin rotation (delta = 0) was used. Analysis was conducted using pre-specified two and three factor analysis, as opposed to using Eigenvalues greater than one, due to the small number of questions. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity were used to test adequacy of the analysis. The minimum loading of an item was 0.32. (223) Mean rank scores (± SD) of the nine questions also allowed comparison with the highest score denoting the most important question.

3.4 Results

The survey had an initial response from 106 participants, but 17 participants did not provide any information, leaving 89 (84%) potentially valid responses. Fifteen responses had inconsistent answers in the reverse questions and so were felt not to be suitable for analysis. Therefore, 74 (70%) valid survey responses were analysed.

Demographic responses including age, gender, income levels were optional, although most respondents completed this section. Table 3-1 illustrates participant background demographics.

Table 3-1 Participant background demographics

Demographic variable	Number	Percentage (%)
Age (n = 72)		
18-21 years	0	0
22-30 years	3	4
31-40 years	9	13
41-50 years	8	11
51-60 years	18	25
61-70 years	18	25
71-80 years	14	19
81-90 years	0	0
>90 years	2	3
Gender (n = 72)		
Male	20	28
Female	52	72
Ethnicity (n = 71)		
Asian other	3	4
Black African	1	1
Black British	3	4
Chinese	1	1
Indian	4	4
White British	45	63
Mixed	3	4
Other	11	15
Income (n = 53)		
£0	0	0
£0 – 9,999	9	17
£10,000 – 24,999	15	28
£25,000 – 49,999	18	34
£50,000 – 74,999	6	11
£75,000 – 99,999	1	2
> £100,000	4	8

Respiratory conditions (n = 74)		
COPD	17	23
OSA	12	16
Asthma	38	51
Lung cancer	1	1
ILD	6	8
Bronchiectasis	14	19
Long-COVID	5	7
Other*	11	15
2-diseases	19	26
3-disease	4	5

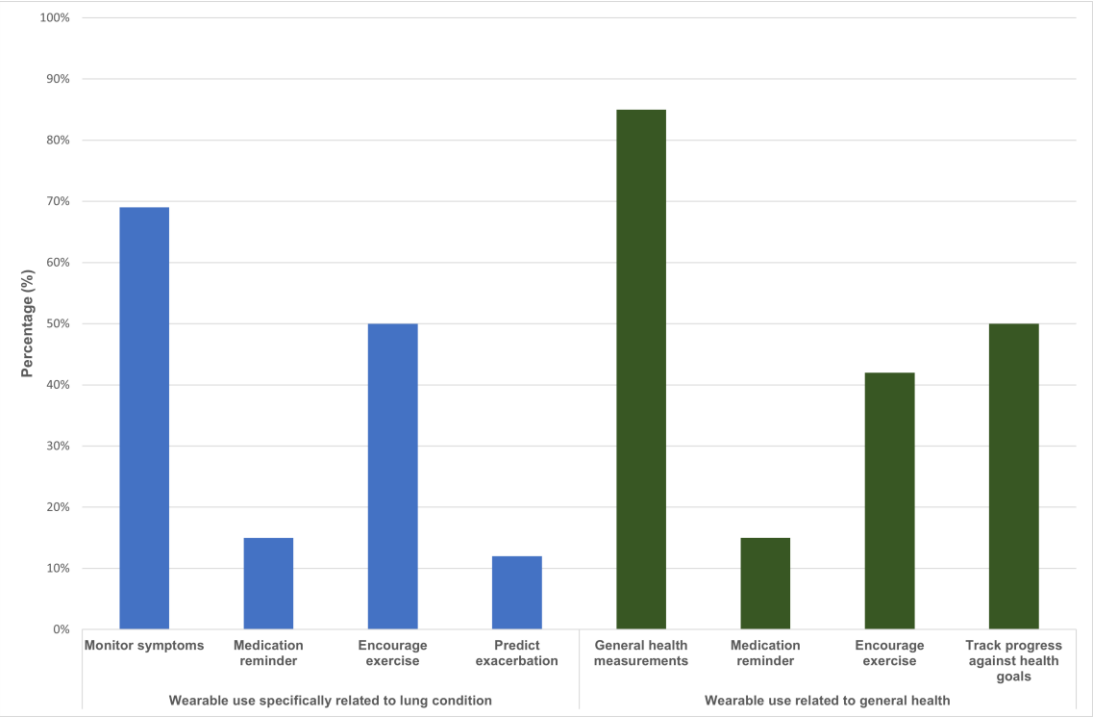
Abbreviations: COPD = chronic obstructive pulmonary disease; ILD – interstitial lung disease; OSA = obstructive sleep apnoea.
*included non-tuberculous mycobacteria, allergic broncho-pulmonary aspergillosis and sarcoidosis.

3.4.1 Participants already using wearable technology

Overall, 26/74 (35%) of participants currently used a wearable device. The majority used a smart watch (58%), with 27% using a Fitbit, and 4% used a smart ring. No participants currently used a pedometer or any other wearable device. Participants utilised their wearable device specifically in relation to their lung condition as well as for their general health. Figure 3-3 illustrates the different reasons participants utilised their wearable device.

Binomial logistic regression analysis looking at whether age (<50 years vs. >50 years), gender (female vs. male), and annual income (<50,000 vs. >£50,000) were associated with current use of wearables, found no significant differences with respective odds ratios (OR) of 0.76 (0.20 – 2.9), 2.31 (0.63 – 8.4), 0.91 (0.21 – 3.9).

Figure 3-3 Percentage of participants and different uses of their wearable device.



Only 16 participants answered the question relating to whether they find their wearable device useful to monitor their health. 56% either agreed or strongly agreed that they found the device useful, while 19% either disagreed or remained neutral.

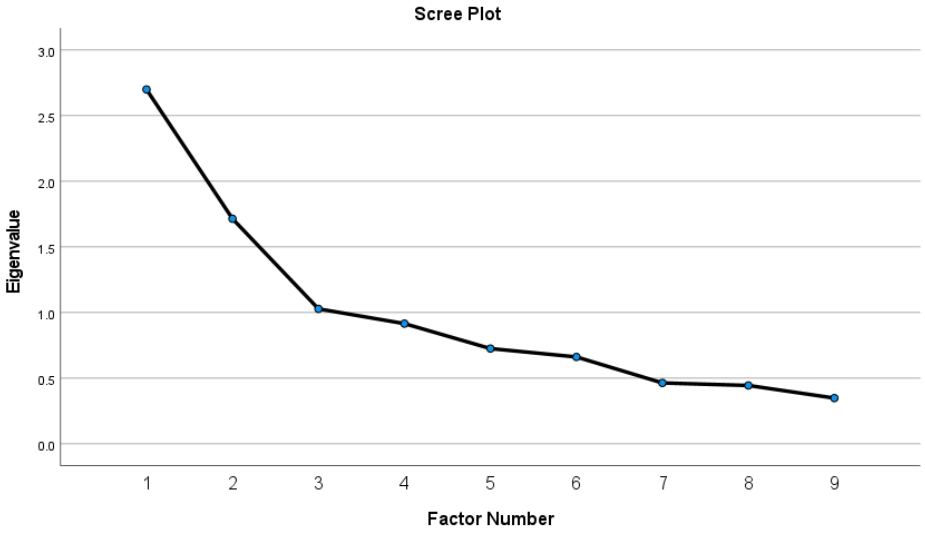
3.4.2 Exploratory factor analysis

Exploratory factor analysis was conducted on the nine remaining Likert-scale questions. Cronbach's alpha for the 74 valid questionnaires was 0.65.

The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was 0.667, and Bartlett's test of sphericity rejected the null hypothesis ($p<0.001$). Three factors had an Eigenvalue above 1 and explained 60% of the variance. When selecting how many factors to include in a model, researchers must balance parsimony (a model with relatively few factors) and plausibility (enough factors

to adequately account for correlations amongst the measured variables). Figure 3-4 shows the Scree plot.

Figure 3-4 Scree plot for the 9 items as part of exploratory factor analysis.



Maximum likelihood ratio and direct oblimin rotation used (delta 0)

Exploratory factor analysis with both 2 and 3 fixed factors were performed. Table 3-2 and Table 3-3 illustrate the rotated pattern matrix.

Table 3-2 Pattern matrix with 2 factors and loading correlations.

Question	Factor	
	1	2
I would like to learn about new technology that I can wear.	0.665	
Wearable technology will increase my confidence to monitor my long-term lung condition at home.	0.630	
I believe that wearable technology will reduce the number of times I see a doctor of my community team, in relation to my lung condition.	0.607	
I think that the wearable technology that is currently available is accurate.	0.478	0.338
It is important the wearable technology links to other devices that I use to monitor my health.	0.584	
It is important the wearable technology has undergone testing in an appropriate clinical trial and has been approved by regulatory bodies.		
The wearable technology should look the same as other everyday items so that other people don't know I am wearing it.		0.750
I think wearable technology will become a normal part of everyday life in the future.	0.363	-0.490
I am more likely to use wearable technology if I have the support from my friends and family.	0.402	

Extraction Methods: Maximum Likelihood; Rotation Method: Oblimin with Kaiser normalisation.

Table 3-3 Pattern matrix with 3 factors and loading correlations.

Question	Factor		
	1	2	3
I would like to learn about new technology that I can wear.	1.014		
Wearable technology will increase my confidence to monitor my long-term lung condition at home.			0.428
I believe that wearable technology will reduce the number of times I see a doctor of my community team, in relation to my lung condition.			0.719
I think that the wearable technology that is currently available is accurate.			0.506
It is important the wearable technology links to other devices that I use to monitor my health.	0.387		
It is important the wearable technology has undergone testing in an appropriate clinical trial and has been approved by regulatory bodies.			
The wearable technology should look the same as other everyday items so that other people don't know I am wearing it.		0.952	
I think wearable technology will become a normal part of everyday life in the future.		-0.371	
I am more likely to use wearable technology if I have the support from my friends and family.			0.527

Extraction Methods: Maximum Likelihood; Rotation Method: Oblimin with Kaiser normalisation.

3.4.3 Mean rank scores for Likert-scale questions

For the nine Likert scale questions Table 3-4 shows the mean rank scores in descending order, such that the first ordered question was the most agreeable to participants.

Table 3-4 Mean rank scores presented in descending order.

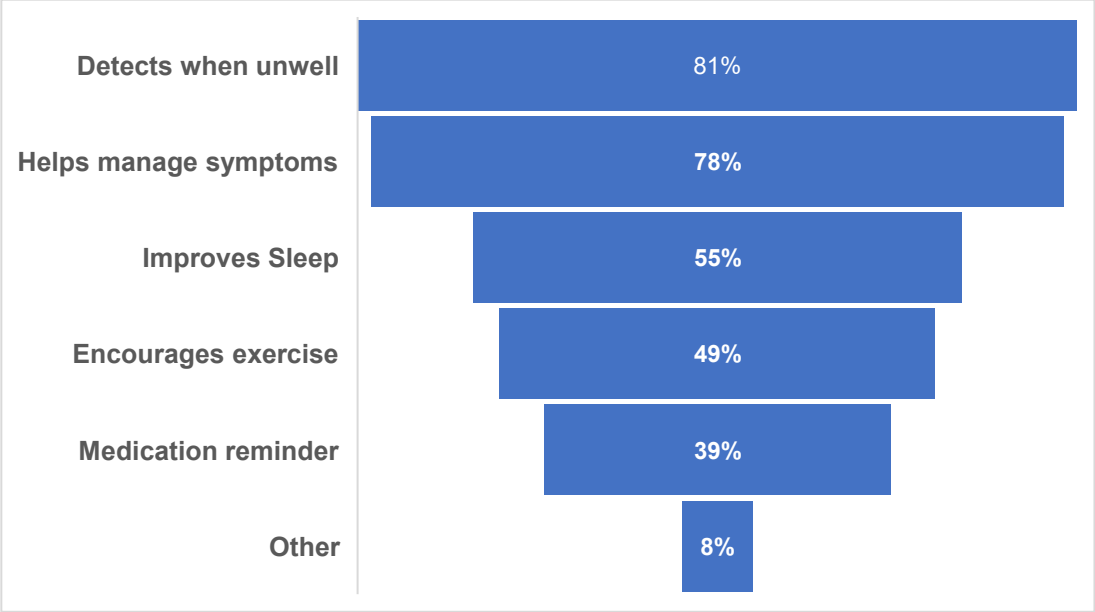
Question	Theme	Mean score (SD)	Positive scores (%)	Negative scores (%)
It is important the wearable technology has undergone testing in an appropriate clinical trial and has been approved by regulatory bodies.	Product characteristics	6.4 (0.8)	99	0
I would like to learn about new technology that I can wear.	Attitudes to technology	6.3 (1.0)	93	2
Wearable technology will increase my confidence to monitor my long-term lung condition at home	Attitudes to technology	6.2 (0.9)	95	0
It is important that the wearable technology links to other devices that I use to monitor my health	Product characteristics	5.8 (1.0)	85	0
I think wearable technology will become a normal part of everyday life in the future.	Social influence	5.8 (1.3)	88	5
I believe that wearable technology will reduce the number of times I see a doctor of my community team, in relation to my lung condition.	Attitudes to technology	5.3 (1.2)	74	4
I am more likely to use wearable technology if I have the support from my friends and family.	Social influence	5.1 (1.1)	57	0
The wearable technology should look the same as other everyday items so that other people don't know I am wearing it	Social influence	5.0 (1.6)	63	14
I think that the wearable technology that is currently available is accurate	Attitudes to technology	4.7 (1.0)	51	6

For each question, scores of 5-7 were considered as positive scores, which meant respondents agreed with the item and scores of 1-3 were considered as negative scores. Scores of 4 were neutral values and so not included in the percentages.

3.4.4 Product characteristics

Several questions asked the participants about their ideal product characteristics. Participants were asked how wearable technology would be useful to them with several options described (Q11). Figure 3-5 illustrates their response.

Figure 3-5 Participants response when asked how wearable technology would be useful to them (n=74)



Participants were also asked to identify three characteristics of a future wearable device that would be most important to them (Q13). 44 participants incorrectly answered this question by either choosing more or less than three characteristics. Therefore 30 valid samples were available for analysis. Figure 3-6 illustrates the commonest characteristics picked by participants in descending frequency (n = 30).

Participants were also asked how they would prefer to access the information from the wearable technology. The funnel chart is illustrated in Figure 3-7.

Figure 3-6 Most important characteristics of wearable technology.

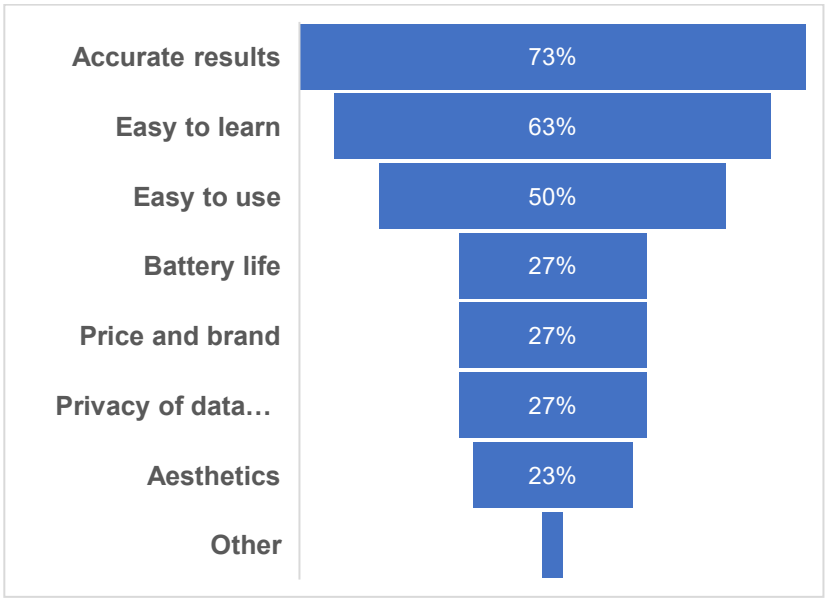
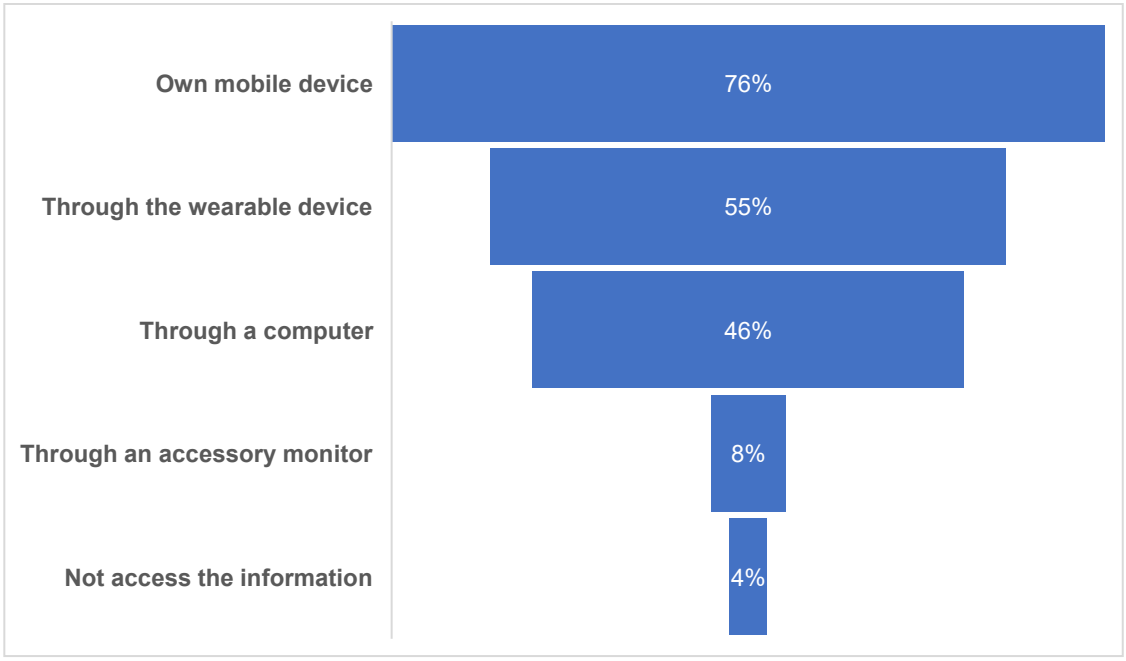


Figure 3-7 Participant preferences in accessing information from wearables.



The remaining questions about product characteristics were Likert-scale questions and have been summarised in Table 3-4.

3.4 Discussion

This survey on wearable technology in patients with chronic lung diseases had a 70% completion rate with 74 valid responses. The survey demographic was representative of a typical age distribution of patients seen in chronic respiratory disease clinics at a London tertiary hospital, with about 50% of participants being between 50 and 70years old. The majority of respondents were female (72%) and from a white British ethnic background. Most participants earned less than £50,000. While there was a good spread of different chronic respiratory diseases, the majority had obstructive airways disease with 51% of participants diagnosed with asthma. A quarter of the participants had two different chronic respiratory diseases.

About a third of the respondents currently used a wearable device, giving insight into potential user characteristics. This is similar to previously published data by Chandrasekaran et al, who found that 30% of adults in the United States use wearable health devices (224). Smart watches and Fitbit devices were the commonly used devices and participants utilised the device to monitor their symptoms (69%) through measurements (like saturation and breathing rate) but also used the device for general health measurements (85%). Most participants used the device to encourage them to exercise (50%) and track their progress against health goals (50%), but few used the devices as a reminder for their medication (15%). Just over half of these patients agreed that they found the device useful, while 19% disagreed or remained neutral.

While the previous survey by Chandrasekaran et al. concluded that older adults (>50years) were less likely to use wearable devices compared to 18-34

years (OR 0.46 – 0.57 (224)), our survey found no difference during binomial logistic regression (OR 0.76 (0.20 – 2.9, p=0.69). This is unsurprising, given most respondents in our survey were above 50 and our overall sample size was small and not normally distributed.

Cronbach's alpha for the nine Likert-scale questions was satisfactory at 0.65. (225) The KMO was 0.667 suggesting that it was possible to conduct exploratory factor analysis (EFA). EFA with a two-factor solution showed several cross-loading items suggesting inadequacy of this solution. EFA with a three-factor solution, led to two factors having only two items which is generally considered weak and unstable in the literature. Therefore, overall, for this dataset, EFA was not a helpful analysis tool. (223) This is likely to be due to the presence of a small sample size and a small number of Likert-scale questions.

Participants ranked the importance of wearables undergoing testing and approval by regulatory bodies the highest, with 99% agreeing with this item (mean rank score 6.4). This is important, given most wearables currently in the market have not undergone rigorous testing and therefore lack reliability and accuracy. (226) Moreover, some participants seemed to be aware of this, as only 51% (mean rank score 4.7) agreed that currently available technology is accurate. However, it is important to note, a large number remained neutral suggesting a lack of knowledge. This was similar to findings by Sun et al, who found that their respondents expressed a negative attitude towards accuracy of personalised health devices used for chronic diseases. (213)

The survey questions were based around four different themes, common and central to previously described models of technology acceptance and social behavioural theory. User characteristics are important when developing novel technologies. Most responses were from patients with obstructive airways diseases (including asthma, COPD and bronchiectasis), which are some of the most common chronic lung diseases seen, suggesting that novel technology should focus on these conditions, given the technology is likely to be benefit the majority of users. Most current users of wearables wore watches, suggesting a preference for this type of wearable, echoing findings by Keogh et al, (209) and preferred using the device to monitor symptoms, improve general health and engage in physical activity.

Participants attitudes towards technology are important. A population that is technology averse, will not be receptive to new technology, meaning reduced behavioural intention, fewer early innovators and therefore less 'diffusion' of technology within the target population. (219) However, this survey has shown most participants were agreeable to learning about new technology (mean rank score 6.3), felt the technology would increase their confidence to monitor their condition (mean rank score 6.2) and felt wearables would reduce the number of times they see their doctor (mean rank score 5.3). This is promising, as it suggests participants with chronic lung disease have a positive attitude to technology and are likely to be receptive to new wearables in the future.

Product characteristics are important when developing a device that will have longevity and perceived usefulness. Participants agreed that the wearable should be tested rigorously and be approved by regulatory bodies (mean rank score 6.4) and also felt it should link to other devices that they use to monitor

their health (mean rank score 5.8). The majority of patients attending hospital wanted wearables to detect when they become unwell (81%), help manage their symptoms (78%) and improve their sleep quality (55%). When asked to identify the three most important characteristics of future wearables, participants wanted a device that was accurate (73%), easy to learn (63%) and easy to use (50%). These characteristics are similar to those concluded by Sun et al. (213) They were less concerned about data privacy (27%) and aesthetics (23%). Finally, they wanted a device that linked to their own mobile device so that they could access the information from the wearable (76%). Very few wanted the information through an accessory monitor (8%).

Social norms and peer pressure impact the 'diffusion' and acceptance of new technology. While most participants agreed that wearables will become a normal part of everyday life in the future (88% positive score), fewer participants agreed that they are more likely to use wearables if their family supported them (57%), with the rest remaining neutral. This suggests that for this population, family support in use of wearables is not as important. This is in contrast to findings by Sun et al. who found that social support was an important factor in driving use. This difference is likely to be due to the population surveyed. Sun et al. surveyed a Chinese population, where they found family support was important as they have a interdependent relationship with others. (213) This may not be the case in the British population we surveyed. This highlights important socio-cultural differences and also means novel technology providers need to be aware of population self-construals.

There were several limitations to this survey. Firstly, the majority of respondents were of white British ethnicity, and therefore the views of ethnic

minority communities were not represented. This is important, as this population is often harder to engage in clinics and healthcare due to several barriers including language. Furthermore, their social construct may differ, and therefore opinions around social norms and peer pressure impact are also likely to differ. Second, the survey had few Likert-scale questions to allow for accurate exploratory factor analysis. While the initial survey had a larger number of questions, the expert patient-panel at Asthma-UK/BLF felt the length of the survey was too long. Third, the survey had small numbers and a complete response rate of 70%. A large number of online participants did not answer any questions following consent. However, in the literature, a response rate of above 60% is considered acceptable. (227) Fourth, the survey did not have many open / free-text questions which may have allowed better expression of participants' views on wearable technology and allowed for qualitative thematic analysis. Fifth, online surveys inherently have a self-selection bias and can have sampling limitations with difficulty reaching certain populations.

In conclusion, this survey on the acceptability of wearable technology for long-term respiratory disease, has highlighted that patients are open to the idea of wearable devices in the future that are accurate, easy to use, easy to learn and approved by regulatory bodies. While there was no direct question about cost, most participants of this age group had low-middle income earnings, meaning any new technology should be affordable, and focus on helping patients manage their symptoms and detect when they become unwell. Participants were less concerned about making the wearables look like everyday items and prioritised functionality over aesthetics. This survey will

help future developers of technology in producing a wearable for this patient population, increase the chance of patient acceptability and thus usefulness.

Having appreciated that patients would like wearables that are accurate, easy to use and approved by regulatory bodies, the next chapter studies the use of a novel wearable device (AcuPebble RE100) in a group of both stable and exacerbating COPD patients to assess its capability of detecting physiological signals and differences, the utility of these measurements, and understand its acceptability in this population.

CHAPTER 4

4. Chapter 4 – Physiological signal variability differences between stable and exacerbating chronic obstructive pulmonary disease patients: a feasibility and acceptability study

4.1 Background

The data investigating the role of wearable technology and COPD exacerbation detection has had mixed outcomes, and further work in this field is necessary to find simple, practical wearables to identify differences between stable and exacerbating patients, such that future algorithms can be developed to detect change and institute management early.

To detect an exacerbation with novel technology, one first has to understand key differences in physiological parameters measured in a stable population and exacerbating population. Identifying differences, allows the building of algorithms to detect the point at which a stable patient starts to exacerbate, thus allowing for earlier intervention. This study aims to acquire physiological signals including heart rate, respiratory rate and airflow with a novel small wearable device (AcuPebble RE100) in a group of stable and exacerbating COPD patients.

4.2 Aims

The primary objective of this feasibility and acceptability study was to get physiological signals including heart rate, respiratory rate, and airflow with a small new wearable device (AcuPebble RE100) in a group of stable and exacerbating COPD patients that could be used to objectively differentiate between them.

The aims of this work were:

1. To acquire physiological signals including heart rate, respiratory rate and airflow with a novel small wearable device (AcuPebble RE100) in a group of stable and exacerbating COPD patients.
2. Use linear and non-linear time-series analyses methods to assess the following:
    a. Differences in physiological signal variability between stable and exacerbating COPD patients.
    b. Differences in physiological signal variability amongst patients with different phenotypes of stable COPD patients, specifically looking at:
        i. Airflow severity as assessed by the FEV1 measurement.
        ii. Symptom severity as assessed by validated scoring systems like the COPD Assessment Tool (CAT) and the modified Medical Research Council (mMRC) score.
        iii. GOLD ABE categories
    c. The association of physiological signal variability measures with currently measured admission characteristics including:
        i. Admission national early warning score 2 (NEWS2).

ii. The Rome Criteria for COPD exacerbation severity.

iii. Length of hospital stay

d. Differences in physiological signal variability amongst exacerbating COPD patients at the point of admission vs. discharge vs. post-discharge (i.e., exacerbation recovery).

3. Assess the acceptability and feasability of the wearable device.
4. Compare the physiological signal measurements from stable and exacerbating COPD patients with a historical non-COPD cohort.

4.3 Methods

4.3.1 Ethical approval

This study received ethical approval from the Health Research Authority (IRAS ID: 247489; REC reference 19/NI/0194) and was sponsored by the Royal Free London NHS Foundation Trust, where it was also conducted.

4.3.2 Cohort, inclusion and exclusion criteria

Cohort

This study was conducted on a cohort of COPD patients who attended the Royal Free Hospital NHS Foundation Trust, a tertiary London hospital. Stable COPD patients were recruited from outpatient secondary care specialist COPD clinics and from patients attending pulmonary rehabilitation classes in Camden, London. Exacerbating patients were recruited following their admission to hospital once they were on a medical ward. Participants admitted due to an exacerbation of COPD on any medical ward who met the inclusion criteria were included. The majority of participants were recruited from the respiratory ward. The respiratory ward consists of nursing staff experienced in treating patients with exacerbations of COPD using controlled oxygen therapy and has respiratory specialist physiotherapists.

Inclusion criteria

- Adult patients with a diagnosis of COPD made with an exposure history (> 10pack year smoking history) and/or biomass and/or genetic predisposition (e.g., α-1 antitrypsin deficiency) and spirometry showing a FEV1:FVC <0.7.

Exclusion criteria

- Age <18 or > 80 years.
- Subjects who are were not fluent in English, or who had special communication needs.
- Known allergy to the adhesive dressing.
- For the stable patient group, subjects with physical or mental impairments who would not be able to use the new technology on their own.
- For the exacerbating patient group, subjects needing non-invasive ventilation or an admission to intensive care.
- Subjects with very loose/saggy skin in the neck area which would unavoidably result on AcuPebble RE100 swinging if moving the neck.
- Subjects with implantable devices
- Subjects with known sleep disordered breathing

4.3.3 Study protocol

This was a prospective observational study that was performed at Royal Free Hospital. AcuPebble RE100 was the novel sensor used. Under the scope of this study, AcuPebble RE100 was not used as a medical device, but as an acoustic monitor to acquire acoustic signals to carry out signal processing research. The signal acquisition sensor is CE marked for research.

4.3.3.1 Stable Participants

COPD clinic lists and medical records were screened to identify suitable stable COPD participants who met the eligibility criteria. Stable participants were defined as those who had not an exacerbation for 3 months prior to

recruitment. Potential participants were contacted by telephone and if interested a participant information sheet was either posted or emailed to them, as per participant preference. A follow up conversation with the participant was conducted to see whether they were interested and if so, a study visit was arranged.

Study Visit

Due to the coronavirus pandemic, participants understandably were not keen to come into hospital for a study visit and a decision was therefore made to offer participants a choice of whether to conduct the study visit on the telephone or via a video call through a secure network (NHS Attend Anywhere). If participants chose a remote visit, the following items were posted to the participant, with a pre-paid return envelope for the end of the trial:

1. Written consent form
2. AcuPebble RE100 device
3. Research mobile phone (which was locked for the purposes of the study and contained the AcuPebble COPD application only)
4. Adhesive stickers
5. Charging cables
6. Usability questionnaire for the end of study

For the purposes of this study, participants only had to use AcuPebble RE100 whilst they slept for up to 30 days. Written consent was taken.

Baseline data was collected via a case report form (CRF) during the study visit (remote or in-person) that included the following information:

- Baseline demographics including age, gender, ethnicity and body mass index.
- Smoking history
- Lung function tests / spirometry details
- NICE COPD severity
- Modified Medical Research Council (mMRC) dyspnoea score
- COPD Assessment Test score
- GOLD ABCD category
- Past medical history
- Drug history
- Social history: mobility aid requirement and package of care

During this study visit (remote or in-person) the following steps were taken to set participants up with AcuPebble RE100:

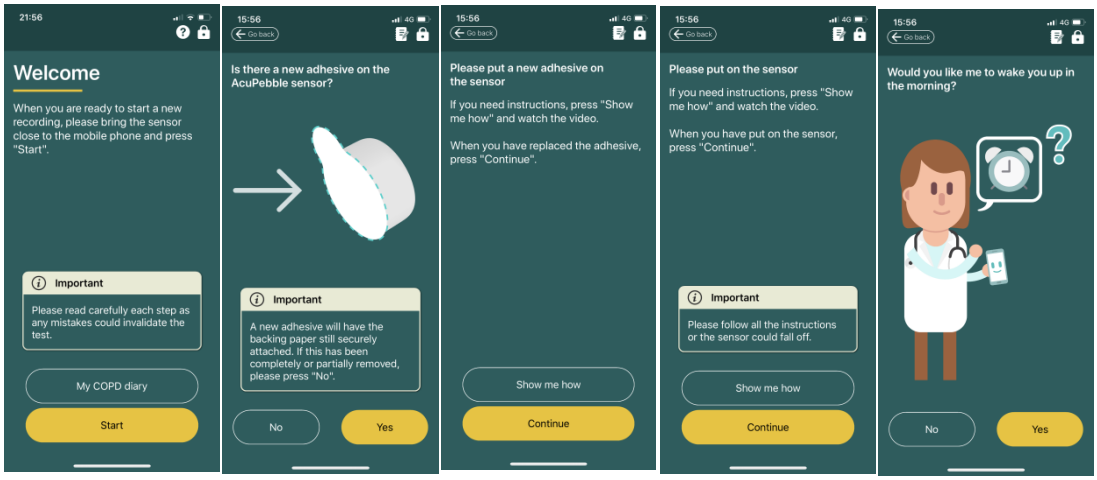
1. The participant was initially shown how to link the AcuPebble RE100 device with the mobile phone by having the device near the phone and pressing the ‘start’ button.
2. The participant then needed to attach AcuPebble RE100 onto their neck using the adhesive sticker, anywhere between the suprasternal notch and Adam’s apple.
3. While the mobile phone application had videos showing participants how to do this, we went through the following steps to ensure participants were comfortable with this step. The adhesive stickers had a ‘yellow’ and ‘white’ side. Participants were asked to remove the ‘yellow’ side first and place the device on the exposed surface.

Following this, they were asked to remove the ‘white’ side, leaving a clear sticky surface which attached to their neck.

4. Once the device was on the neck, participants had to press a ‘start recording’ button. They also had to ensure the device and mobile phone were no more than 1m apart to ensure adequate signal strength.
5. In the morning, participants were told to press ‘stop recording’ and follow the steps on the mobile phone application to ensure the data was uploaded automatically to a GDPR compliant cloud. The signals were encrypted and pseudo-anonymised.
6. The participant was then asked to repeat the above steps nightly (with a new adhesive sticker) for up to 30 nights.
7. They were reminded to charge the device and mobile phone to ensure enough battery for the following night.

Figure 4.1 shows a pictorial version of the steps above. (Reproduced with approval from Acurable Ltd).

Figure 4-1 Steps taken to set up AcuPebble RE100 with the mobile phone



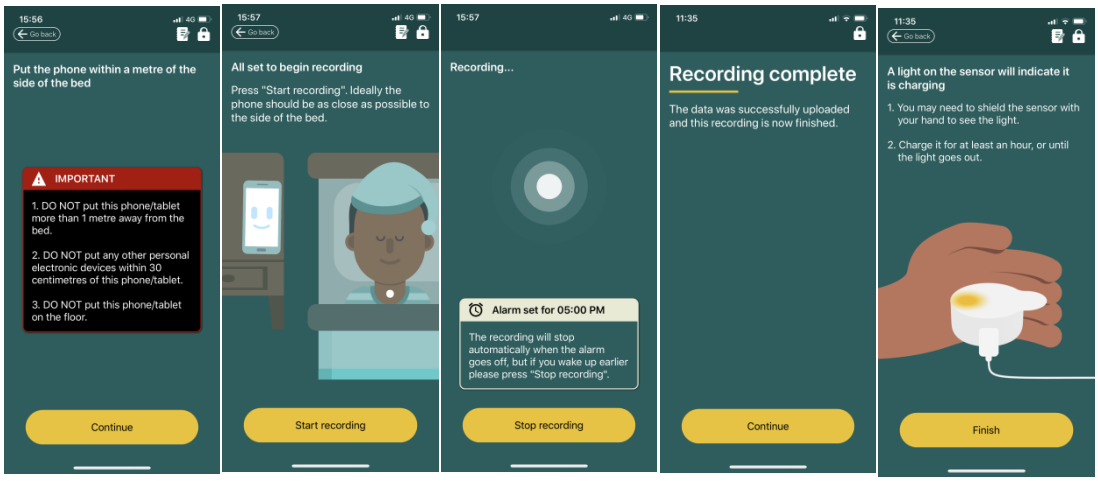
Step 1: Main home screen – participants press start with pebble near.

Step 2 – Participants would tick 'no' to this

Step 3 – Participant puts on a new adhesive on the sensor

Step 4 – Participants puts the sensor on their neck

Step 5 – Participants were asked whether they wanted an alarm in the morning.



Step 6 – A brief warning about device / phone position

Step 7 – Participants start recording

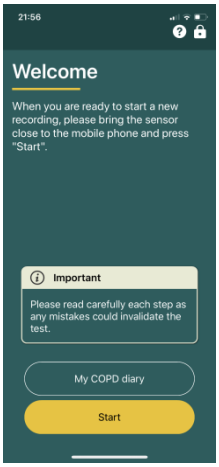
Step 8 – Participants stop recording in the morning

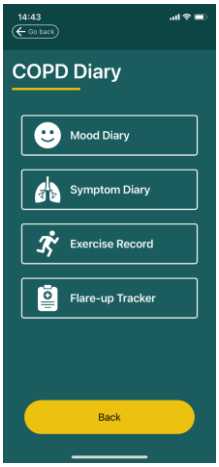
Step 9 – recording is uploaded

Step 10 – Participant reminded to charge device

The second part of the mobile phone application was a ‘COPD diary’ which participants were asked to complete daily (Figure 4-2)

Figure 4-2 COPD diary.

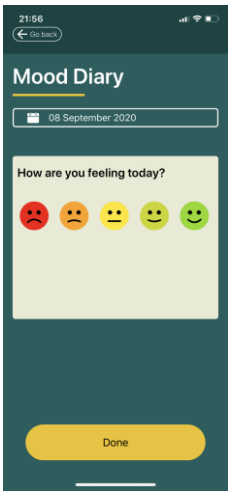


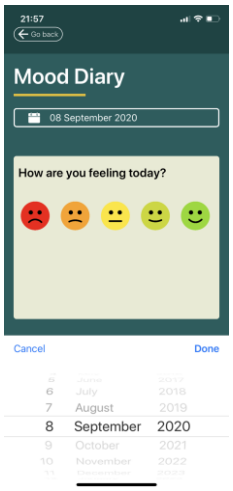


The following four items formed part of the diary:

1. Mood diary: this was one question asking participants to pick their mood daily as shown in Figure 4-3.

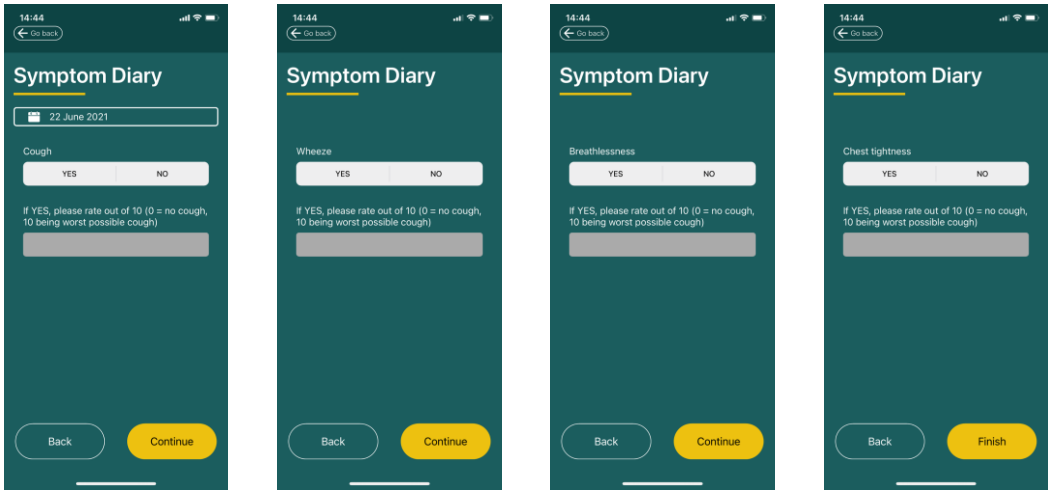
Figure 4-3 Mood diary





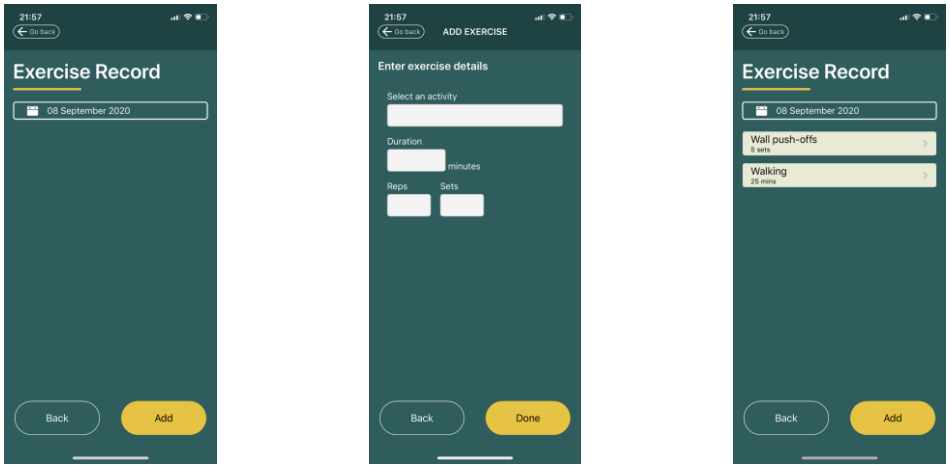
2. Symptom diary: asked participants daily to score (from 0-10) the severity of the following four symptoms (shown in the Figure 4-4):
    a. Chest tightness
    b. Shortness of breath
    c. Wheeze
    d. Cough

Figure 4-4 Symptom diary



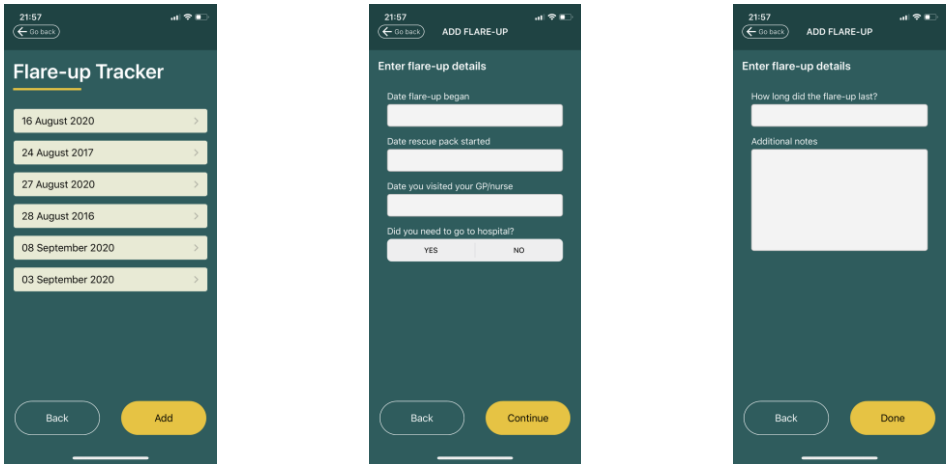
3. Exercise diary: asked participants to note down any exercise they did during the day and the duration and number of repetitions. A group of sample exercises were available to choose on the application to help participants, but they could also add their own. The following exercises were already listed on the application (an example is shown in the Figure 4-5):
    a. Walking
    b. Step-ups
    c. Star jacks
    d. Marching
    e. Sit to stand
    f. Wall push-offs
    g. Heel raises
    h. Arm punches
    i. Squats
    j. Bicep curls
    k. Hip extensions
    l. Upright rows
    m. Knee extensions
    n. Leg side to side
    o. Mini knee lifts
    p. Other

Figure 4-5 Exercise diary example



4. Flare-up tracker (Figure 4-6): participants were asked to fill this section in only if they had a flare-up requiring either:
    a. Use of their rescue pack at home
    b. Attendance to their general practitioner
    c. Attendance to accident and emergency
    d. Admission to hospital

Figure 4-6 Flare-up tracker

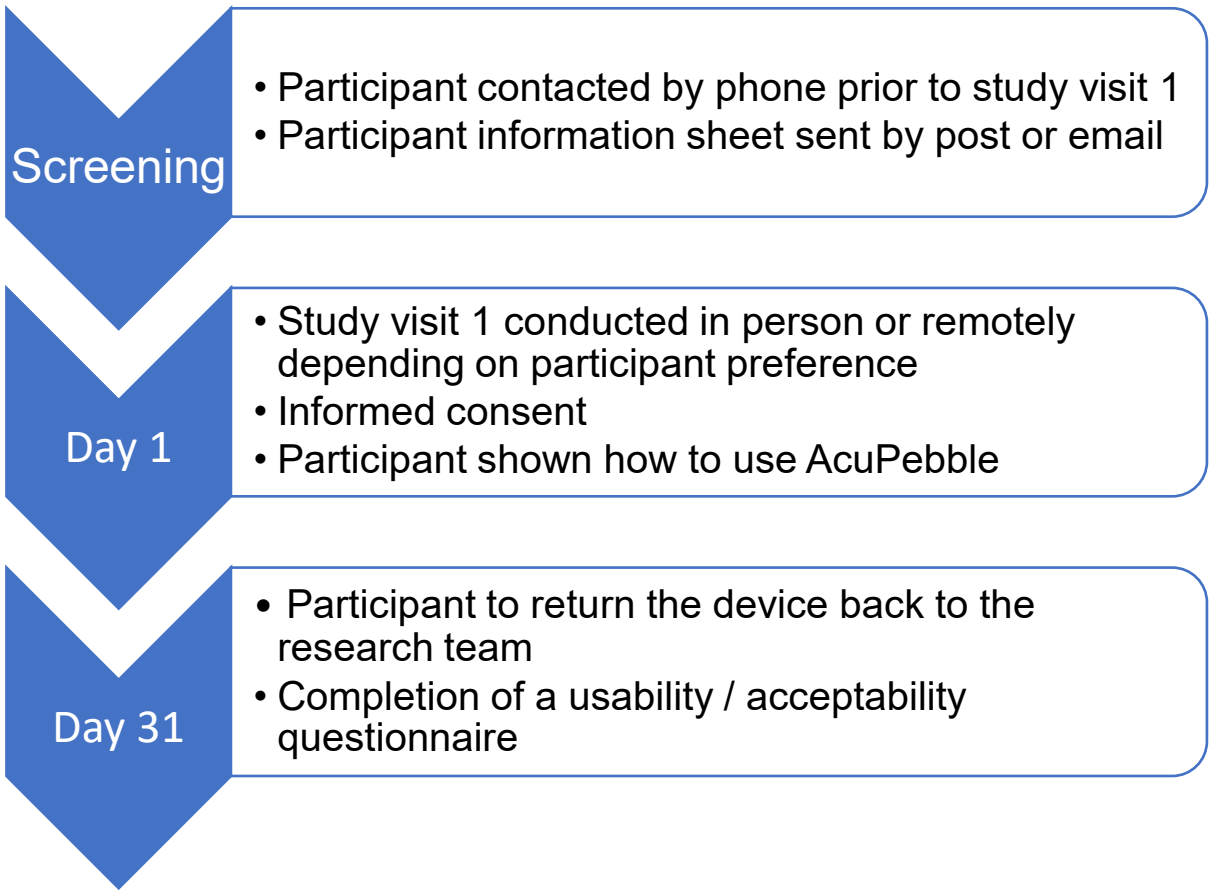


Participants were asked to continue to wear the device during any ‘flare-ups’ or exacerbations.

If participants preferred to keep a paper diary, this option was also available to them.

At the end of study, participants were asked to return the equipment with the consent form (if study visit was remote).

Study flow chart: Stable patients



4.3.3.2 Exacerbating Participants

For the inpatient / exacerbating group of participants, medical admission lists were screened to identify suitable patients. Patients who had moved from the accident and emergency department to any medical ward were approached and the study explained to them. If interested a participant information sheet was given to them. Patients on intensive care and those needing non-invasive ventilation were not approached.

Participants who were interested and had read the information sheet were then asked to complete and sign a written consent form.

Participants were asked to wear AcuPebble RE100 throughout the duration of their inpatient stay. Participants were recruited from any medical ward during their admission. If agreeable to continue, participants were asked to use the device while asleep post discharge for up to 28 days. The initial protocol had specified up to five days post discharge, however, following the recruitment of the first ten patients, we noticed that 3 patients had had a re-admission within a month. To capture this data for future patients, an amendment was added to the protocol and participants were asked to wear the device for 28 days post discharge. This time frame was chosen as it was felt to be clinically relevant as the NHS does not receive additional payment for recurrent COPD exacerbation admissions within this time frame. (228)

All participants admitted to any medical ward were given the following during their inpatient stay:

1. Two AcuPebble RE100 devices – this was to ensure there was enough battery to last the patient 24 hours. One AcuPebble RE100 device carried enough charge for 12-14 hours.
2. Research mobile phone (which was locked for the purposes of the study and contained the AcuPebble COPD application only)
3. Adhesive stickers
4. Charging cables

Baseline data was collected via a case report form (CRF) that included the following information:

- Baseline demographics including age, gender, ethnicity and body mass index
- Smoking history
- Lung function tests / spirometry details
- NICE COPD severity
- Medical Research Council dyspnoea score (32)
- COPD Assessment Tool score (29)
- GOLD ABCD category
- Past medical history
- Drug history
- Social history: mobility aid requirement and package of care
- Admission arterial blood gas (if done)
- Admission CXR (if done)

Participants were then shown how to connect AcuPebble RE100 to the mobile phone. (Figure 4-1). The research team facilitated connecting and attaching

the AcuPebble RE100 sensor twice daily if necessary for the duration of the participants admission.

Inpatients were given a daily paper diary to fill in which had the following information:

- Walked to the toilet
- Using a commode
- Physiotherapy sessions
- Self-exercise
- Cough + sputum production
- Amount of sputum (+ / ++ / +++)
- Given a nebuliser
- Eating

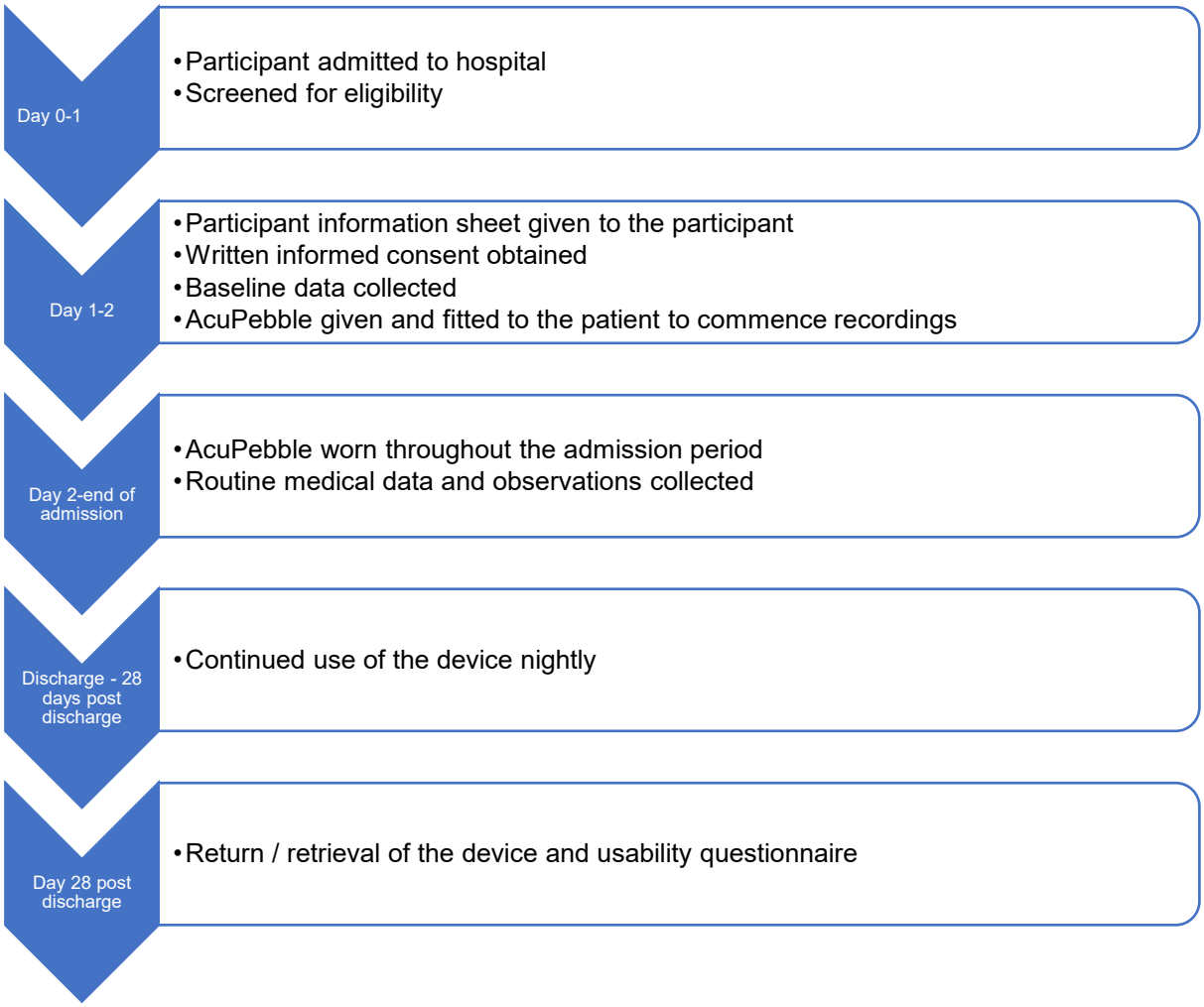
Throughout the admission daily clinical data was also collected from the participant records including:

- Exacerbation medication including antibiotics, steroids, nebulisers, and the timing of these.
- Nursing observations throughout the day including oxygen saturations, respiratory rate, heart rate, blood pressure, temperature and NEWS2 score.
- Participant clinical status – defined simply as static, deteriorating, or improving.
- If the participant was on a ward monitoring system this was also collected

On discharge participants were asked whether they would be happy to take the device home for a further 28 days. At home they were asked only to wear the device while sleeping and asked to start completing the same COPD diary as the stable patients on the mobile phone application.

Following 28 days, the participants were asked to return the device, either in person, or were provided with a pre-addressed return envelope. The participant was also asked to complete a usability questionnaire.

Study flow chart: exacerbating group



4.3.3.3 Historical cohort without COPD for comparative group

To enable direct comparison with a cohort without COPD, (non-COPD group), using the same device, historical data were used. AcuPebble SA100 has previously been validated as a diagnostic tool for obstructive sleep apnoea (OSA) by our research group. (145) For that prospective study (IRAS ID 225818, REC Ref 18/LA/0308), patients attending the sleep and ventilation clinic for evaluation of possible OSA at Royal Free London Hospital NHS Foundation Trust were asked to use AcuPebble SA100 alongside a multi-channel sleep study (clinical standard). Patients used these devices simultaneously. AcuPebble SA100 data gave the same time series data (HR, RR and airflow) as well as automatically diagnosing OSA (through detection of apnoeas and hypopnoeas and giving an anponea/hypopnoea index (AHI)). The multi-channel sleep study included a pulse oximeter and therefore gave HR data. However, did not give direct RR measurements.

It is important to note that AcuPebble SA100 is a device that is similar to AcuPebble RE100 and works in the same way, recording acoustic signals and converts them to heart rate (HR), respiratory rate (RR) and airflow data. The main difference is AcuPebble SA100 is CE marked for OSA diagnosis while AcuPebble RE100 is intended for research purposes only. While for the remainder of the chapter they are referred to as either AcuPebble SA100 or RE100 depending on which device was used, the results and interpretation are transferable between the devices.

Patients with a normal sleep study and therefore no OSA were defined as having an AHI < 5 events/hr. Their HR, RR and airflow time-series data was extracted and analysed using the same algorithms and methodology as described below. This provided me with a historical non-COPD cohort, that I could use to compare with the results from the stable and exacerbating COPD population. As for the stable patients, a six-hour nocturnal recording was used (excluding the first 10-minutes) giving the same number of data points. The detailed analysis plan is described below.

4.3.4 Linear and non-linear analysis methodology and data analysis plan.

AcuPebble RE100 senses acoustic signals and manufacturer algorithms convert these into heart rate (HR), respiratory rate (RR) and airflow. In terms of the accuracy of these measures, HR has a root mean squared error (RMSE) of 3.62 beats per minute when the heart rate range is 50-120 beats per minute. (148). Bland Altman plots have shown that for RR there is a bias of -0.215 breaths per minute and limit of agreement between -5.747 to 5.316 breaths per minute (unpublished). The device gives HR and RR data every 2 seconds, a resolution of 0.5Hz. The device gives airflow data every 0.1 seconds, a resolution of 100Hz. This in turn means there are 100 data points every second.

Therefore, physiological signal variability analysis was conducted on three independent time-series, HR, RR and airflow. Given the significant resolution differences between airflow and the other signals, different analysis methods were employed. Both linear and non-linear methods were used for the HR and RR data. However, given the high resolution of the airflow data, detrended fluctuation analysis (DFA) was felt to be a more appropriate analysis technique for the airflow data. Further details, definitions and explanations of physiological signal variability measures can be found in the Appendix (Chapter 7.1). The linear and non-linear analysis method used in this study are described below.

For the stable COPD group, we assessed any associations between physiological signal variability measures and:

1. Severity of airflow obstruction based on FEV1.
2. The GOLD ABE assessment tool.
3. Symptom burden severity based on the CAT score and mMRC breathlessness score.

For the exacerbating group any associations between physiological signal variability measures with currently measured admission characteristics were also analysed including:

1. Admission national early warning score 2 (NEWS2)
2. The Rome Criteria for COPD exacerbation severity.
3. Length of hospital stay

For the non-COPD group, the HR measures from the multi-channel sleep study (done on the same night as AcuPebble SA100), were also extracted and analysed using similar algorithms as described below. This was to assess whether HR variability measures from two different devices (AcuPebble SA100 and gold standard multi-channel sleep study) were comparable. The pulse oximetry used as part of the multi-channel sleep study had a higher resolution of HR data (3Hz) with 3 samples every second. The data was then filtered (by averaging adjacent data points) to decrease the resolution to both 1Hz (1 sample every second) and 0.5Hz (2 samples every second). The latter (0.5Hz) was to directly compare to the AcuPebble SA100 data which was also at this resolution. The code used for this work is in the Appendix (Chapter 7.5)

All data analysis was conducted in MATLAB programming software with the help and guidance of Dr Alireza Mani and the Network Physiology Laboratory at University College London.

4.3.4.1 Linear Analysis methods for HR and RR data

Given the large number of data points available for analysis, to deal with missing data, the data were first cleaned to remove potential artefact:

- HR – any measurement below 40 beats per minute, was assumed to be inaccurate data capture, and this measurement was changed to the median HR.
- RR – any measurement below eight breaths per minute was assumed to be inaccurate data capture, and this measurement was changed to the median RR.

The percentage of artefact for each trace was noted and if any recording had ≥15% of aberrant data, that study was not included in the final analysis. For included studies the following measurements were calculated.

The mean HR and RR were calculated.

With the HR measurements the R-R interval (ms) was calculated by Equation 2 equation. (229)

Equation 2: Calculation of R-R interval from heart rate measurements. (229)

$$R - R\ interval = \frac{60{,}000}{HR}$$

With the RR measurements the breath-to-breath interval (B-B) (ms) was calculated by Equation 3.

Equation 3: Calculation of breath-to-breath interval from respiratory rate measurements

$$B - B\ interval = \frac{60{,}000}{RR}$$

Using both the R-R interval and B-B interval, the standard deviation of these intervals was calculated giving linear time-domain measure for each (SDNN and SDBB respectively).

Monfredi et al showed that the R-R interval (for HR) has an inverse non-linear relationship with HR and therefore ideally the SDNN should be corrected for the mean HR to reduce bias and improve reliability. This value (cSDNN) is shown in Equation 4. (230)

Equation 4: Correction of SDNN by Monfredi et al. (230)

$$\mathrm{cSDNN} = \frac{\mathrm{SDNN}}{e^{-\frac{HR}{58.8}}}$$

Therefore, for the HR data the cSDNN was also calculated. No such correction exists for the RR time series.

4.3.4.1 Non-linear analysis methods used for HR and RR data

For all non-linear analyses the calculated R-R and B-B intervals was used, rather than the original HR and RR time-series, as this is conventional methodology in the literature. (231) This also allows comparison of my data to other published literature.

The SD1 and SD2 values from the Poincare Plots and SE were calculated from well described and freely available coding algorithms in MATLAB processing software. For SE calculations I used settings of *m* at 2 and *r* at 0.2. These values of m and r are widely used in the existing literature and are accepted as the standard. Further explanations of Poincare plots and sample entropy can be found in the Appendix (Chapter 7.1)

Multi-scale entropy (MSE) was also calculated for both HR and RR using well described and freely available coding algorithms in MATLAB processing software. For this analysis, MSE was used over ten scales with *m* at 2 and *r* at 0.2.

All the code used for this work can be seen in the Appendix (Chapter 7.1).

4.3.4.3 Time series duration for HR and RR analysis

There are limited data on nocturnal physiological variability analysis and no current gold standard duration of analysis recommended for COPD linear and non-linear analysis. However, previous work on heart rate variability has described long term (24 hours), short-term (≈ 5minutes) and ultra-short-term (<5 minutes) analysis, which are not interchangeable. It is also well recognised that longer term analysis will enable better representation of the overall response of a system. (231)

When comparing nocturnal readings from several patients with stable COPD, a fixed time-series duration was necessary to avoid bias and improve comparability. Six hours was felt to adequately represent all the stages of sleep and give more than enough data points (10,800) to conduct physiological variability analysis. Studies with less than six hours of recording were deemed too short and excluded from the analysis. When patients had more than six hours of recording, only the first six hours were analysed (excluding the first 10 minutes), so that the same time-series duration was used in all patients. Within this time period, if the patient had broken sleep, but left the device on and it continued to record valid data, it was included. If there was no recording or the signal dropped for a few minutes, this data was treated as missing data.

If a time-series had ≥ 15% of total data missing, this was excluded from the analysis.

However, given the data derived from AcuPebble is novel, I also sought to understand whether hourly analysis of our data in the stable COPD group (across 6 hours) was comparable to analysing the entire 6-hour period of recording. This concept is shown below.

An example showing the calculated sample entropy (HR) for a random night from one participant, hourly and over the entire 6-hour period.

Hourly sample entropy (SE)

Hour 1	*Hour 2*	*Hour 3*	*Hour 4*	*Hour 5*	*Hour 6*
0.1991	*0.2415*	*0.1811*	*0.2585*	*0.1694*	*0.33314*

Mean hourly SE (calculated from each hour above) = 0.2302

6-hourly SE from the same entire recording period = 0.2658

This comparison was performed on all the recordings for the first five participants. If the 6-hourly recording had ≥ 15% of data missing, this recording was removed. Additionally, for each hour, if there was ≥ 15% of data missing this individual hour was removed for that night. The mean hourly value was calculated from the remaining hourly data available and used to compare with the overall 6-hourly data.

Following the identification that a six-hour nocturnal time window was adequate in the stable COPD population, the same time window was used to analyse the exacerbating population. The exacerbating group had recordings available throughout their stay (both day and night), however, for

comparability, we chose to only use the nocturnal recording portion. However, it is important to note, that the recordings encompassing the nocturnal portion, often started in the late afternoon/evening. Therefore, we could not take six hours from the start of the recording. To reduce bias, the median start time of all the stable valid six-hour nocturnal recordings was calculated and used as the start time for the exacerbating population. This was to ensure a similar time and duration of the recording, thus increasing comparability. The first valid nocturnal recording within 48 hours was used to compare with the stable group.

Recordings from admission to discharge and post discharge were also compared where available. To do this, the first valid nocturnal recording within 48 hours of admission was compared to a nocturnal recording 48 hours from discharge. This was then also compared to a nocturnal recording 5-days post discharge. Where 5-day recordings were not available, day 4 or 6 was used instead. A small number of participants used the device for longer than 5 days post discharge and this was also analysed in a similar manner.

When comparing the admission night, discharge night and post-discharge night, the same technique as above was used (i.e., the median start time of the home recordings was used as the starting point). For the post-discharge nights, participants understandably only started the recording when they went to sleep, which in some cases was later than the median start time used. In this situation their actual sleep time was used for the recording analysis (similar to the home stable patient analysis).

4.3.4.4 Airflow data analysis

The airflow data had a high resolution of 100Hz, meaning there were 100 data points every second. Using the same 6-hour time window as the HR and RR analysis, this gave 2,160,000 data points. The data were initially cleaned to remove potential artefact. If there was a 30 second apnoea (determined by 3000 data points where the airflow was recorded as 0), this was deemed to be artefact and thus deleted.

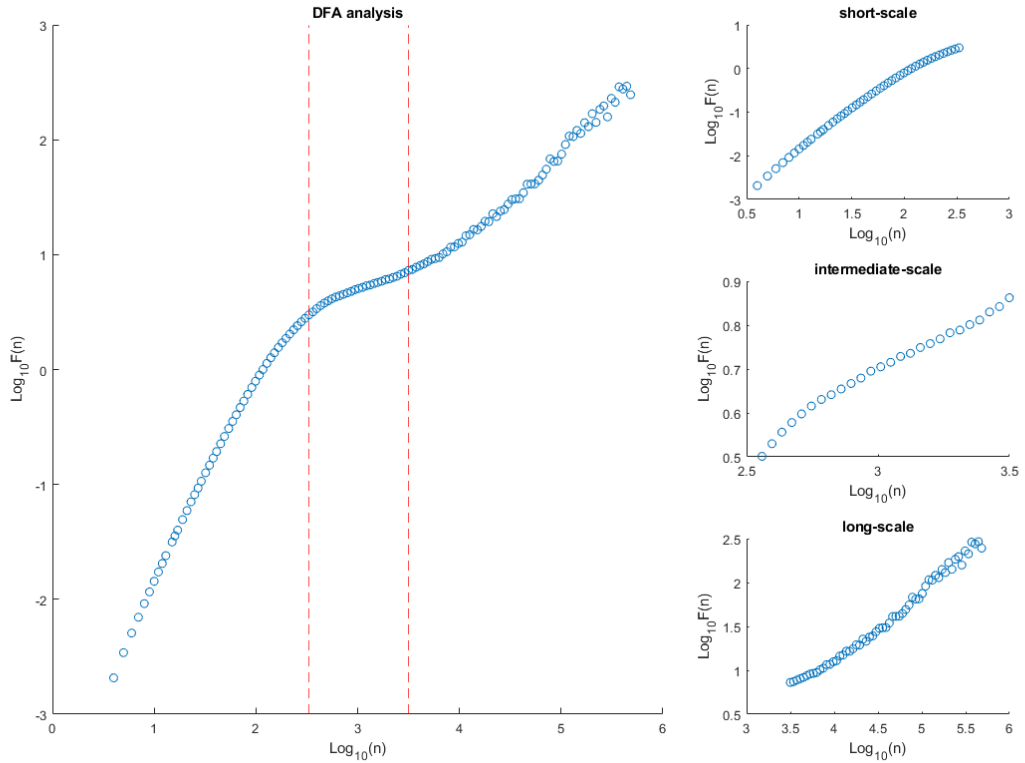
Detrended fluctuation analysis (DFA), a non-linear method, was used to analyse this data., DFA analyses a time-series at various scales, de-trends the data and then calculates the fluctuation at each time scale. (Appendix 7.1) This is plotted on a double logarithmic axis and the exponent of the straight line is denoted as alpha (α). Therefore, in a DFA plot, the logarithm of fluctuation (Log10 f(n)) is plotted against the logarithm of scale (n). (123) There have been few studies previously looking at airflow using DFA, with one focussed on a sleep apnoea population (232) and another isolated peak flow readings. (233) Previous studies have shown that both oxygen saturation and heart rate (234) DFA graphs have one 'cross-over' point. Initial analysis of our airflow data showed two 'cross-over' points suggesting a short-term, intermediate term and long-term scaling exponent, α1, α2 and α3 respectively. These were calculated separately by visually inspecting the DFA graph and identifying the cross-over point manually.

The first three airflow recordings for the first five patients (total of 15 recordings) in the stable group were all inspected manually and found to have similar cross-over points. An example of this, can be seen below in Figure 4-

7. The same two cross-over points were also seen in the preliminary analysis of the exacerbating group allowing for direct comparison.

It is useful to note, that the first cross over point at a scale of 2.52114 is equivalent to $Log_{10}(332)$ and means that we are looking at the data at a scale of roughly 3 seconds (as we have 100 data points every second). Therefore, α1 is a short-term scaling exponent. The second cross-over point at a scale of 3.49941 is equivalent to $Log_{10}(3158)$ and means that we are looking at the data at a scale of roughly 31 seconds, therefore α2 is an intermediate scaling exponent and there after α3 is a longer scale scaling exponent.

Figure 4-7 Illustration of DFA analysis plot with cross-over points highlighted.



Main graph illustrates the complete DFA analysis results. The dashed red lines depict the two cross-over points. Panels on the right show the various sections of the graph corresponding to short, intermediate, and long scales.

4.3.4 Statistical analysis

Given this was feasibility study and was novel, a sample size calculation was not performed. Initially a sample of 40 participants (20 stable and 20 exacerbators) was deemed sufficient. However, due to the variability of the data we received and the adherence of participants to the device, this was subsequently revised to 70 participants (40 stable and 30 exacerbators).

All statistical analysis was conducted using the software Statistical Package for the Social Sciences (SPSS). Baseline demographic data between different groups of patients was compared using Chi Squared tests for ordinal and categorical data. Continuous data were checked for normality using the Shapiro-Wilk test. For the initial validity work, to ascertain which recording time-period (hourly vs. 6-hourly) was most useful, we performed Bland Altman Plots and calculated the intraclass correlation coefficients (ICC). As the performance of the same device was being investigated in each patient, absolute agreement and 2-way mixed methodology was used as shown by Koo et al. (235) This method was also employed when comparing the same HR variability measures in the healthy cohort (comparing AcuPebble SA100 with pulse oximetry).

For the main COPD analysis, continuous data from multiple groups were analysed using either the Krushal Wallis H test for non-parametric data or an Analysis of Variance (ANOVA) test for parametric data. Simple linear regression analysis was used to assess the association between two continuous variables and multi-linear regression analysis performed to account for any confounding variables.

For comparing two groups the independent t-test for parametric data or the Mann-Whitney U test for non-parametric data was employed.

When comparing the MSE analysis at varying scales and in two different groups a two-way ANOVA was used.

Overall data was reported as mean (± standard deviation) or median (± interquartile range) based on the mode of distribution. If the physiological parameters were non-normally distributed both mean (± standard deviation) and median (± interquartile range) were presented to allow for adequate comparison of values in the literature.

A p-value of ≤ 0.05 was considered to be statistically significant.

Acceptability of AcuPebble was described based on usability feedback and descriptive parameters.

4.4 Results

For the study, 200 non-selected participants were screened, of which 114 met eligibility criteria, and 59 were consented for the study (36 with stable COPD and 23 hospitalised patients with an exacerbation. Of the 36 stable COPD patients, two participants subsequently declined following consent with no data to analyse, and one participant was found to be ineligible post consent and therefore did not start the study. This participant, post consent was found to have a pacemaker and so had to be excluded. They had not started the study. Therefore 33 participants with stable COPD were analysed (20 male, 13 female) with a mean (SD) age of 67 (10) years.

Of the 23 COPD patients undergoing an exacerbation, five patients did not have enough nocturnal data on a recording within 48 hours of admission. Therefore, 18 participants undergoing an exacerbation were analysed (10 male, 8 female) with a mean age (SD) of 64.5 (9) years.

The historical non-COPD group had 51 patients (29 male, 22 female, mean age (SD) 38 (11) years), who had undergone a one-night study. While all had available RR data, following removal of artefact there were 48 HR recordings and 46 airflow recordings.

Figure 4-8 illustrates the study flow diagram. Table 4-1 shows all the participants baseline characteristics and medical comorbidities. The non-COPD cohort were significantly younger had a lower prevalence of having ever smoked, and significantly fewer comorbid conditions. None of the non-COPD cohort had any form of known airways disease.

Table 4-2 shows the COPD participants' pulmonary function tests, symptom severity scores and relevant medication.

All participants had lung function within 3 years of the study. In some cases, the lung function post study start was taken as it was closest to data analysis.

Table 4-3 shows participant admission data.

Figure 4-8 Study flow diagram for the COPD patients.

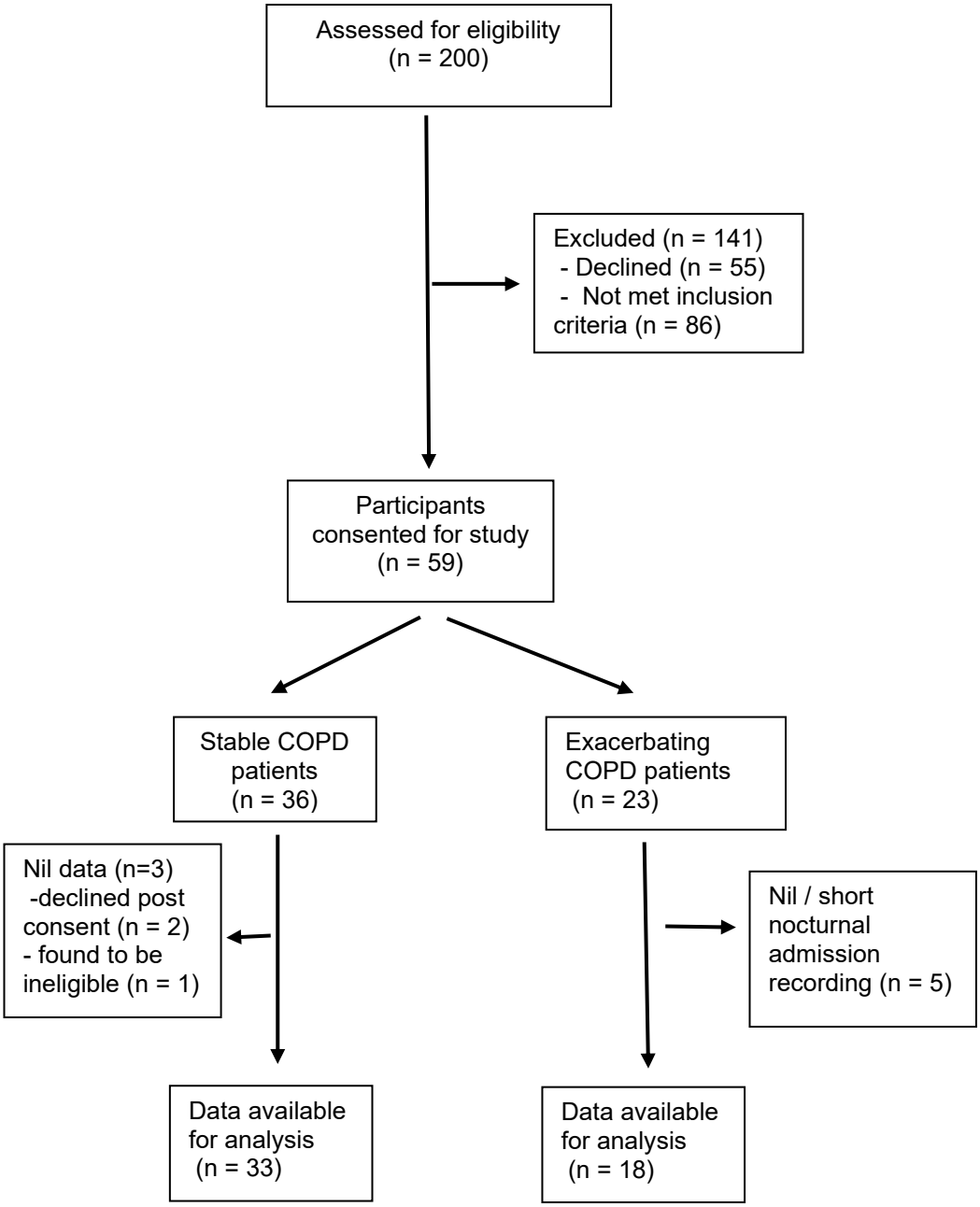


Table 4-1 Baseline characteristics of all participants

Baseline characteristic	**Non-COPD cohort (n = 51)**	**Stable COPD (n = 33)**	**Exacerbating COPD (n = 18)**	**p value ***
Male (%)	29 (57)	20 (61)	10 (56)	0.73
Female (%)	22 (43)	13 (39)	8 (44)	0.73
Age (years) (mean ± SD)	38 ± 11**	67 ± 10	64 ± 9	0.46
Body Mass Index ($kg.m^2$) (median (IQR))	25.2 (23.5 – 28.9)	27.1 (21.0 – 31.8)	18.9 (17.7 – 24.5)	**0.002**
Current smoker (%)	8 (15)**	6 (18)	7 (39)	0.11
Ex-smoker (%)	12 (24)**	27 (82)	11 (61)	0.11
Pack year history (median (IQR))	Not available	47 (25 – 64)	43 (40 – 50)	0.97
Mobility (%) Independent Uses a stick Uses a frame	Not available	 20 (61) 11 (33) 2 (6)	 13 (72) 4 (22) 1 (6)	0.69
Independent with regards to activities of daily living (%)	Not available	31 (94)	18 (100)	0.29
Medical Co-morbidities (%)				
Alpha-1 Antitrypsin	Not available	4 (12)	0	0.12
Atrial fibrillation	0	3 (9)	0	0.19
Cerebrovascular disease	0	0	0	-
Hypercholesterolaemia	1 (2)**	9 (27)	5 (28)	0.97
Hypertension	5 (10)**	11 (33)	5 (28)	0.68
Ischaemic heart disease	1 (2)**	5 (15)	2 (11)	0.69
Oxygen therapy	Not available	2 (6)	1 (6)	0.94
Peripheral vascular disease	0	1 (3)	0	0.46
Type 2 diabetes mellitus	1 (2)**	5 (15)	1 (6)	0.31

*p-value shows significance between the stable and exacerbating COPD patients. **denotes significance ($p < 0.05$) between the non-COPD cohort and stable COPD patients.

Table 4-2 Pulmonary function tests, baseline symptom severity assessment scores and relevant medication

Characteristic	Stable group (n = 33)	Exacerbating group (n = 18)	p value
Pulmonary function tests* (mean ± SD)			
FEV1 (L)	1.35 ± 0.64	0.91 ± 3.22	**0.008**
FEV1 %predicted	48.96 ± 20.00	32.31 ± 10.14	**0.002**
FVC (L)	3.27 ± 1.06	2.42 ± 0.68	**0.004**
FVC %predicted	91.31 ± 25.67	70.00 ± 19.97	**0.005**
FEV1/FVC ratio	0.41 ± 0.12	0.38 ± 0.11	0.47
TLCO (mmol/min/kPa)	4.11 ± 2.34	2.46 ± 0.63	**0.023**
TLCO %predicted	48.60 ± 22.82	33.21 ± 10.78	**0.029**
KCO (mmol/min/kPa)	0.86 ± 0.35	0.65 ± 0.18	0.06
KCO %predicted	61.88 ± 25.52	48.72 ± 16.02	0.10
Symptom assessment questionnaires (median (IQR))			
mMRC breathlessness score	3 (2 – 3)	3 (2.5 – 4)	0.25
COPD Assessment Test (CAT) score	20 (14 – 25.25)	27 (22.5 – 32.25)	**0.004**
COPD Severity Assessment (GOLD) (%)			
GOLD A	2 (6)	0	**0.003**
GOLD B	20 (61)	3 (17)	**0.003**
GOLD E	11 (33)	15 (83)	**0.003**
Respiratory Medication (%)			
SABA	33 (100)	18 (100)	-
LABA/ICS	0	1 (6)	0.17
LAMA alone	0	1 (6)	0.17
LABA/LAMA**	10 (30)	1 (6)	**0.040**
LABA/LAMA/ICS**	21 (64)	15 (83)	0.14

*All participants had lung function within 3 years of the study. In some cases, the lung function post study start was taken as it was closest to data analysis. Note one patient had lung function 5 years prior to study but did not have any valid data and so was not included. **Included patients on various combinations, but receiving all the medication.

Table 4-3 Admission data for participants undergoing a COPD exacerbation (n = 18)

Characteristic	**n (%), mean ± SD, median (IQR)**
Length of stay (days)	5 (3 – 7)
Respiratory rate (bpm)	26 ± 7
Heart rate (bpm)	105 ± 17
Oxygen saturations (%)	91 ± 6
Admission NEWS2 score	5 (3 – 6)
Severity (ROME proposal):	
Mild	7 (39)
Moderate	11 (61)
Severe	0
PaO2 (kPa)	7.79 ± 1.28
PaCO2 (kPa)	5.81 ± 1.07
C-reactive protein	54 ± 66

4.4.1 Accuracy and usability of the data recorded by AcuPebble RE00 in the stable COPD group

Participants were asked to wear the AcuPebble RE100 device at night for up to 30 nights. Participants used the device for a median of 18 nights (IQR 10 – 26; range 2 – 34). Participants used the device for a median of 8.3 hours (IQR 6.8 – 9.8; range 0.78 – 13.6) per night. Recordings shorter than six hours duration were not included in the final analysis, leading to a removal of 14% of the recordings (Table 4-4).

Data recordings that had ≥ 15% of missing data, due to device artefact, were not included in the overall analysis. AcuPebble RE100 had less device artefact when recording respiratory rate compared to heart rate and airflow data, meaning that a higher number of respiratory rate data recordings were available for the final analysis. This is summarised in Table 4-4. Overall, there was a total of 338 nocturnal heart rate, 492 nocturnal respiratory rate and 345 airflow recordings from the 33 patients. The median number of recordings available for each patient were 8 (3 – 15) nights, 14 (9 – 23) nights and 8 (3 – 18) nights for heart rate, respiratory rate and airflow respectively.

Table 4-4 Accuracy and usability of the data derived from AcuPebble RE100 in 33 stable patients with COPD.

Participant number	Total number of recordings returned	Number of recordings of <6hour duration	Number of 6-hour HR recordings with ≥15% missing data	Number of 6-hour RR recordings with ≥15% missing data	Number of 6-hour Airflow recordings with ≥15% missing data
RF01	17	2	1	1	4
RF02	24	1	0	0	4
RF03	25	1	16	0	0
RF05	23	0	2	2	2
RF08	3	0	1	0	1
RF09	13	1	0	0	1
RF13	19	0	12	4	19
RF14	23	1	20	0	5
RF15	24	5	0	0	1
RF16	26	2	8	0	19
RF17	4	4	-	-	-
RF18	34	0	7	2	31
RF20	18	10	1	1	2
RF21	25	7	3	0	0
RF22	10	1	8	0	1
RF23	29	6	18	0	21
RF24	34	0	30	0	3
RF31	26	13	0	0	5
RF34	3	1	1	0	0
RF35	18	4	3	0	3
RF36	28	1	3	0	6
RF38	9	6	0	0	0
RF43	29	1	22	16	7
RF45	29	18	6	1	10
RF46	2	1	1	0	1
RF47	28	0	6	0	8
RF48	3	0	0	0	3
RF51	15	1	0	0	0
RF52	23	0	2	0	10
RF53	16	6	2	0	3
RF55	17	0	2	0	3
RF63	7	1	4	0	0
RF64	9	0	2	0	1
TOTAL	**613**	**94**	**181**	**27**	**174**

4.4.2 Comparing hourly and 6-hourly heart rate and respiratory rate analysis in a small group of stable patients.

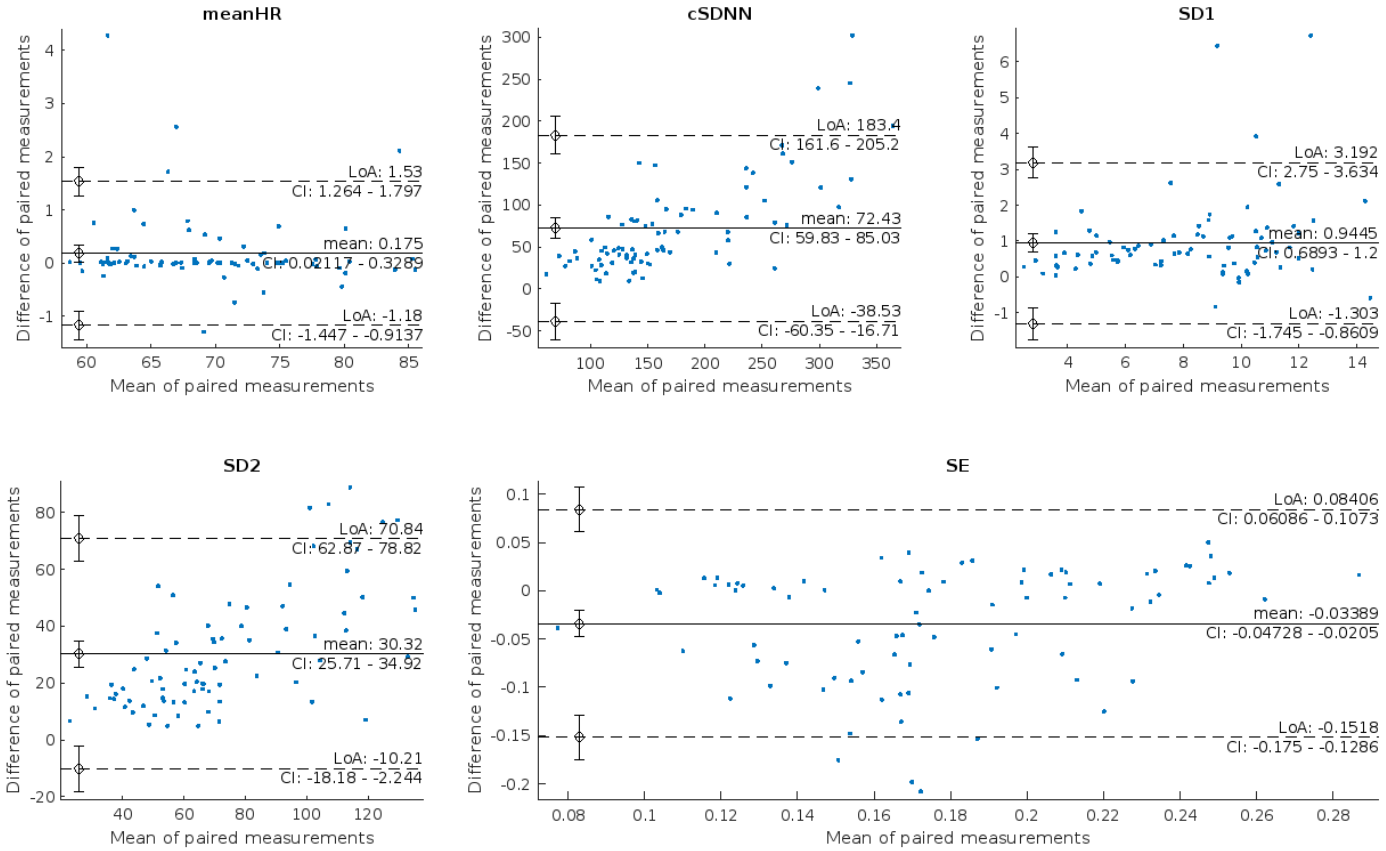
4.4.2.1 Heart rate variability

The Bland-Altman plots comparing the mean hourly vs. 6-hourly data analysis for each of the variables are shown in Figure 4-9 below. The Bland-Altman plots for cSDNN and SD2HR showed that the mean hourly data compared to the 6-hourly data had mean differences (and therefore bias) of, 72ms and 30ms respectively. This suggested that the two approaches were not comparable and may lead to different results. The mean HR, SD1HR and SEHR had more favourable comparable outcomes with lower mean differences and less bias. However, the intraclass correlation coefficient (ICC) values were above 0.7 for all parameters except for SEHR (Table 4-5).

Table 4-5 Intraclass correlation coefficients (ICC) for the hourly and 6-hourly data analysis – heart rate.

Analysis variable	ICC
Mean HR (beats per minute)	0.941
SDNN (ms)	0.737
cSDNN (ms)	0.832
SD1HR (ms)	0.832
SD2HR (ms)	0.735
SEHR	0.640

Figure 4-9 Bland-Altman plots comparing mean hourly and 6-hourly data analysis – heart rate.



Thermoregulation has been shown to play an important role in longer term fluctuations in heart rate variability. (231) This may explain the bias seen in cSDNN and SD2HR measurements, which reflect longer-term fluctuations, given the known changes in body temperature that occur overnight. In view of this, 6-hourly data was thought to better represent the overall variability in nocturnal heart rate compared to hourly data. Moreover, mean hourly data over 6 hours that is then averaged again to give a final value, would have led to a larger standard deviation and potentially less precise data. Therefore, a 6-hour analysis window was used for the analysis of the whole data set.

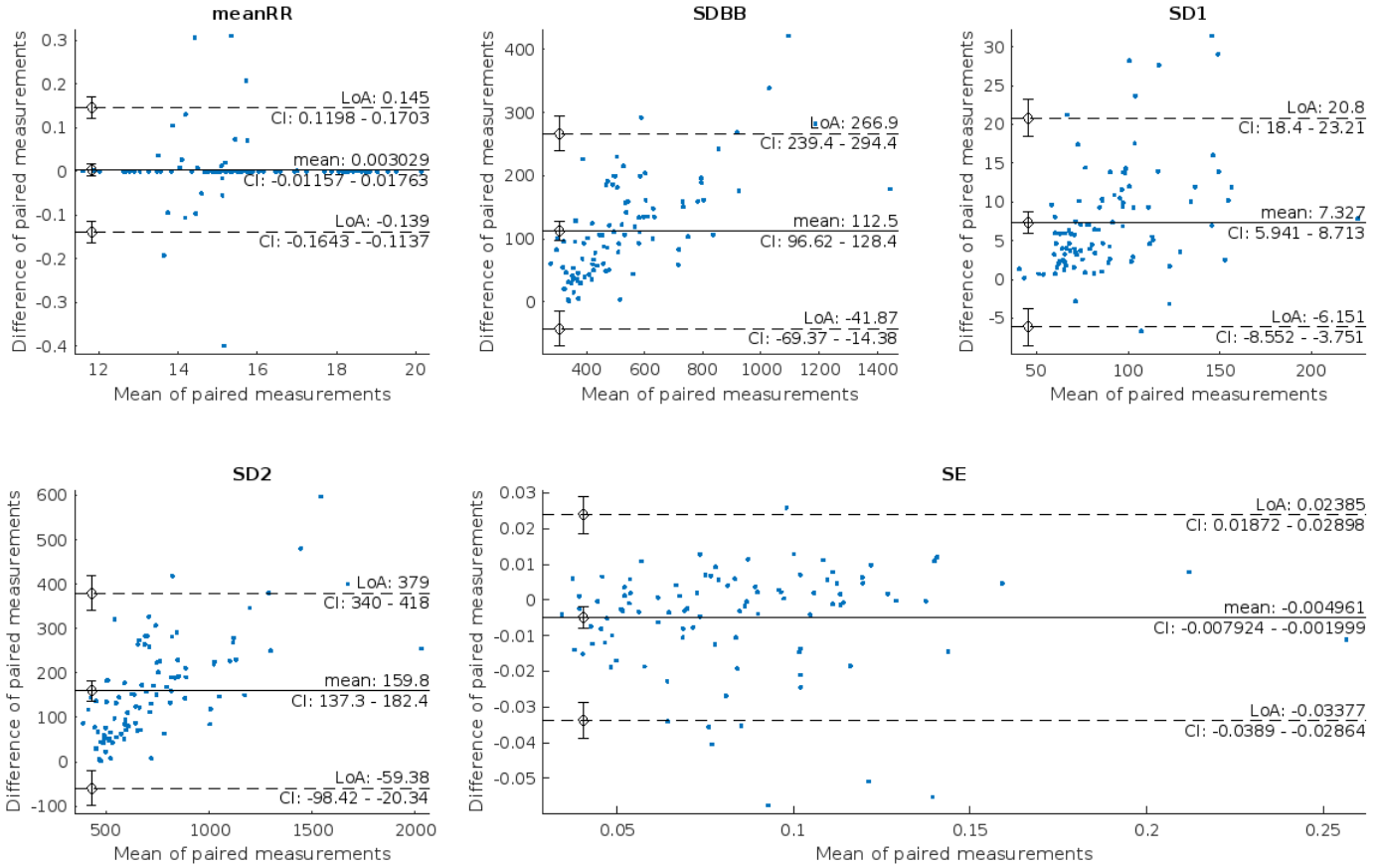
4.4.2.2 Respiratory rate variability

The Bland-Altman plots comparing the mean hourly vs. 6-hourly data analysis (RR) for each of the variables are shown in Figure 4-10. Table 4-6 shows the intraclass correlation coefficients for the hourly and 6-hourly data (respiratory rate) analysis.

Table 4-6 Intraclass correlation coefficients (ICC) for the hourly and 6-hourly data analysis – respiratory rate.

Analysis variable	**ICC**
Mean RR (beats per minute)	0.952
SDBB (ms)	0.767
SD1RR (ms)	0.774
SD2RR (ms)	0.766
SERR	0.757

Figure 4-10 Bland-Altman plots comparing mean hourly and 6-hourly data analysis – respiratory rate.



The Bland-Altman analysis again showed that for SDBB and SD2RR the mean hourly data compared to the 6-hourly data had mean differences (and therefore bias) of 113ms and 160ms respectively. This suggested that the two approaches were not comparable. However, the mean RR, SD1RR and SERR had more favourable and comparable outcomes. Moreover, the intraclass correlation coefficients showed good correlation. In view of the above results, and for ease of comparability of the heart rate data, a 6-hour window was chosen for the remainder of the analysis.

The subsections below describe the results of the analysis of all the heart rate and respiratory rate and airflow recordings conducted over the entire 6-hour period.

4.4.3 Differences in physiological signals (HR, RR and airflow) between all groups (non-COPD, stable and exacerbating COPD patients)

The median start time for AcuPebble RE100 in the group of stable home patients was calculated as 22:39:33. This time was used as the start time in calculating the linear and non-linear time-series measurements for the first valid nocturnal recording within 48 hours of admission for the exacerbating group. Two participants had recordings which fell short of the six-hour time window using this start time. In this case, to maximise data capture, the first quartile start time from the stable COPD patients was used (21:48:21). Data recordings that had ≥ 15% of missing data, due to device artefact, were not included in the overall analysis. Most signals were not normally distributed and therefore non-parametric tests were used and median (IQR) values displayed. The results are illustrated in Table 4-7.

Table 4-7: Differences in physiological signals comparing non-COPD controls vs. stable COPD group vs. exacerbating group.

Physiological variability measure	Non-COPD cohort	Stable COPD group	Exacerbating COPD group	p-value*
Heart Rate (HR) measures (n = 48 vs. 31 vs. 9)				
Mean HR (bpm)	65.48** (60.83 – 70.03)	71.04 (64.55 – 75.10)	74.22 (67.42 – 82.31)	0.35
cSDNN (ms)	189.43 (147.92 – 244.59)	179.40 (162.14 – 245.83)	268.41 (206.67 – 314.90)	**0.006**
SD1HR (ms)	8.90 (6.92 – 10.38)	7.80 (6.52 – 10.40)	12.06 (7.76 – 14.51)	**0.040**
SD2HR (ms)	87.61 (65.73 – 115.35)	74.76 (66.68 – 95.67)	90.18 (78.62 – 130.15)	**0.037**
SEHR	0.1872 (0.1273 – 0.2307)	0.1607 (0.1355 – 0.1981)	0.1258 (0.1044 – 0.1568)	**0.015**
Respiratory Rate measures (RR) (n = 51 vs. 32 vs. 18)				
Mean RR (bpm)	15.67** (14.26 – 17.00)	16.86 (15.13 – 18.87)	18.58 (15.27 – 20.50)	0.30
SDBB (ms)	478.98 (349.30 – 654.93)	525.41 (398.08 – 665.35)	628.68 (514.90 – 1126.30)	**0.024**
SD1RR (ms)	88.93 (69.59 – 126.41)	91.97 (75.97 – 108.82)	133.61 (95.52 – 168.53)	**0.037**
SD2RR (ms)	672.144 (488.23 – 916.01)	737.48 (558.01 – 936.16)	875.93 (722.42 – 1584.36)	**0.025**
SERR	0.0906 (0.0533 – 0.1347)	0.1078 (0.0743 – 0.1377)	0.1378 (0.0982 – 0.1916)	0.09
Airflow analysis (detrended fluctuation analysis) (n = 46 vs. 29 vs. 12)				
Alpha 1	1.6751** (1.6601 – 1.6820)	1.6607 (1.6341 – 1.6730)	1.6294 (1.6055 – 1.6452)	**0.005**
Alpha 2	0.2367** (0.2070 – 0.2661)	0.2805 (0.2600 – 0.3077)	0.2968 (0.2779 – 0.3110)	0.13
Alpha 3	0.7191 (0.6608 – 0.7762)	0.6931 (0.6509 – 0.7931)	0.5000 (0.4676 – 0.5578)	**<0.001**

*p-value shows significance between the stable and exacerbating COPD patients. **denotes significance ($p < 0.05$) between the non-COPD cohort and stable COPD patients.

Heart rate variability

Heart rate variability was analysed for 338 recordings from 31 stable COPD participants and compared to 9 recordings from the exacerbating group and 48 recordings from the non-COPD group. The non-COPD cohort had a significantly reduced mean HR compared to the stable COPD group. There were no significant differences in HR variability and complexity measures between the non-COPD cohort and stable COPD group.

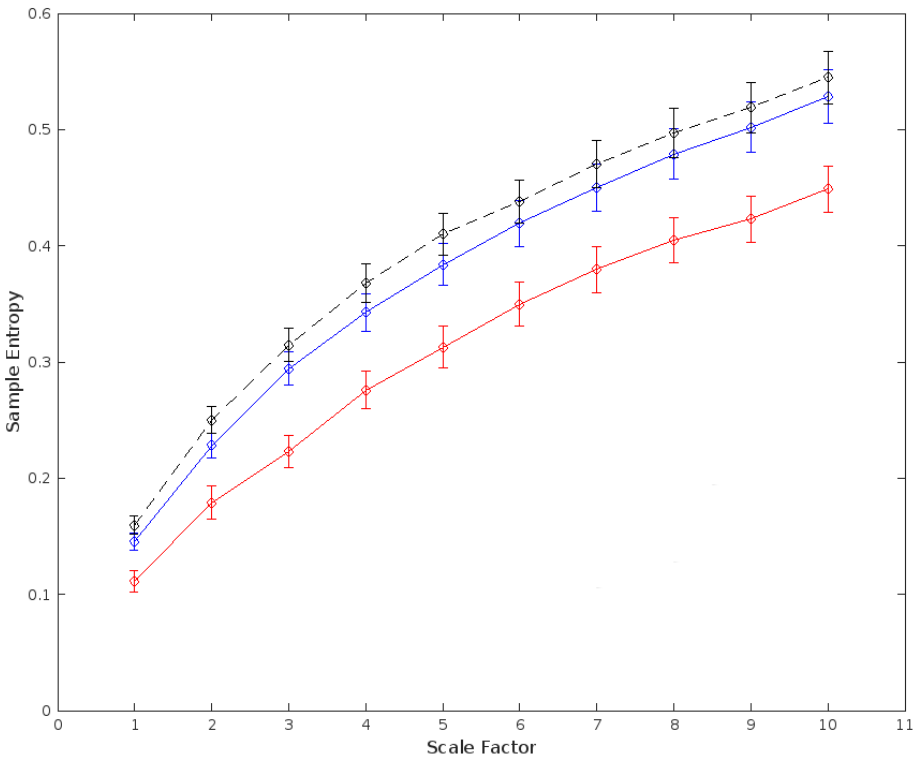
Participants undergoing a COPD exacerbation had significantly higher variability measures (cSDNN, SD1HR and SD2HR) but a significantly lower complexity measure [median SEHR 0.1258 (0.1044 – 0.1568) vs 0.1607 (0.1355 – 0.1981), p = 0.015] compared to the stable group. (Table 4-7)

Multi-scale entropy (MSE) analysis for HR showed that the sample entropy increased as the scale increased for all three groups. The is illustrated in Figure 4-11.

A two-way ANOVA test showed a significant reduction in HR MSE [F_{group} (1,19) = 5.608, p= 0.018, F_{scale}(9,19) = 88.43, p<0.001] in the COPD group compared to non-COPD group, irrespective of scale.

A two-way ANOVA test showed a significant reduction in HR MSE [F_{group} (1,20) = 17.895, p<0.001, F_{scale}(9,20) = 38.37, p<0.001] in the exacerbating group compared to the stable group, irrespective of scale.

Figure 4-11 Heart rate multiscale entropy (MSE) comparing the non-COPD group, stable COPD patients and exacerbating patients.



Black line = non-COPD group; Blue line = Stable COPD group; Red line = Exacerbating COPD group

Respiratory rate variability

Respiratory rate variability was analysed for 492 recordings from 32 stable COPD participants and compared to 18 recordings from the exacerbating group and 51 recordings from the non-COPD group. The non-COPD group had a significantly reduced mean RR compared to the stable COPD group. There were no significant differences in RR variability and complexity measures between the non-COPD group and stable COPD group.

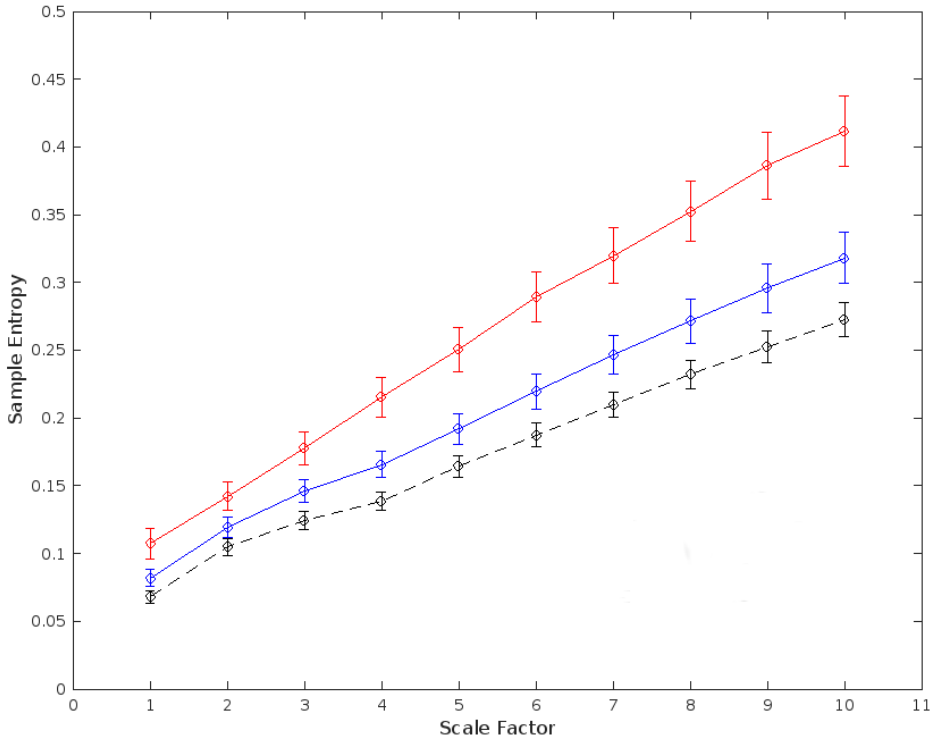
Participants undergoing a COPD exacerbation had significantly higher variability and complexity measures compared to the stable cohort. (Table 4-7)

Multi-scale entropy (MSE) analysis for RR data showed that the sample entropy increased as the scale increased for all three groups. This is illustrated in Figure 4-12.

A two-way ANOVA test showed a significant increase in the RR MSE [$F_{group}(1,19) = 39.89$, $p<0.001$, $F_{scale}(9,19) = 92.13$, $p<0.001$] in the COPD group compared to the non-COPD group irrespective of scale.

A two-way ANOVA test showed a significant increase in the RR MSE [$F_{group}(1,20) = 40.703$, $p<0.001$, $F_{scale}(9,20) = 51.434$, $p<0.001$]] in the exacerbating group compared to the stable group.

Figure 4-12 Respiratory rate multiscale entropy comparing stable COPD to exacerbating patients.



Black line = non-COPD group; Blue line = Stable COPD group; Red line = Exacerbating COPD group

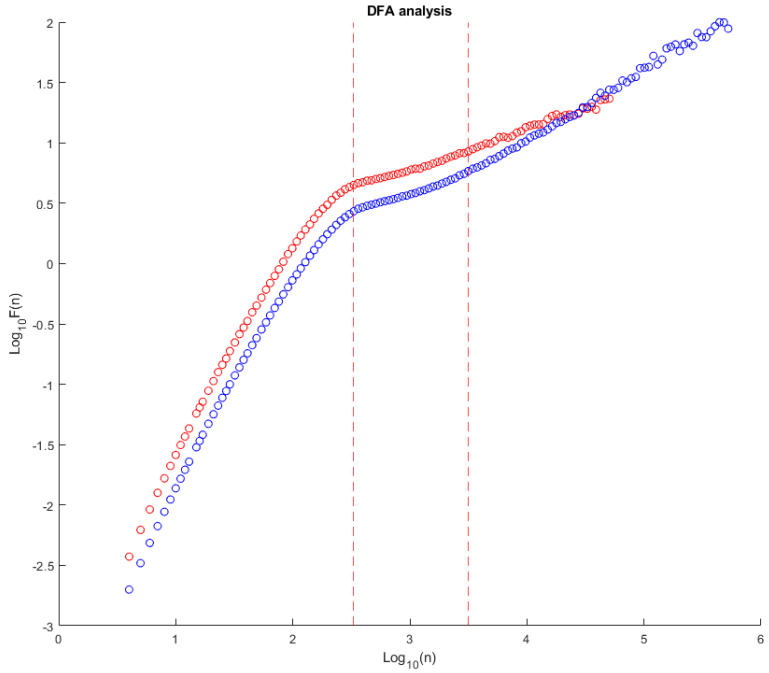
Airflow

Airflow variability was analysed for 345 recordings from 29 stable COPD participants and compared to 12 recordings from the exacerbating group and 46 recordings from the non-COPD group. Airflow variability analysis using detrended fluctuation analysis (DFA) showed the same cross-over points existed in both the exacerbating and stable population, corresponding to a scale of 2.52114 and 3.49941 respectively. The graph shape was also similar. An example comparing a single exacerbating recording alongside a stable recording can be seen in Figure (4-11).

The non-COPD group and a significantly higher median alpha 1 and a significantly lower median alpha 2 compared to the stable COPD group.

The exacerbating group had a significantly lower median alpha 1 and median alpha 3 compared to the stable COPD group (Table 4-7).

Figure 4-13 Example of DFA analysis of a single night from a stable COPD patient and an exacerbating patient.



Exacerbating patients represented by red circles and stable by blue circles.

4.4.4 Physiological signal variability measures in the stable COPD group

4.4.4.1 Heart rate variability measures in relation to the severity of airflow obstruction

Linear regression analysis found no significant associations between FEV1 and mean HR (r = 0.158, p= 0.40), cSDNN (r = 0.155, p = 0.41), SD1HR (r = 0.030, p = 0.87), SD2HR (r = 0.091, p = 0.63) or SEHR (r = 0.035, p = 0.85).

4.4.4.2 Heart rate variability measures in relation to symptom burden

There were no significant differences between heart rate variability measures and different severities of breathlessness as assessed by the mMRC score (Table 4-8). Linear regression analysis found no significant association with the CAT score and mean HR (r = 0.098, p = 0.61), cSDNN (0.151, p = 0.42), SD1HR (0.065, p = 0.74), SD2HR (0.087, p = 0.65) or SEHR (0.212, p = 0.26).

Table 4-8 Heart rate variability measures and different severities of breathlessness

HRV measure	mMRC 0 (n=2)	mMRC 1 (n=6)	mMRC 2 (n=6)	mMRC 3 (n=11)	mMRC 4 (n=6)	P value
Mean HR(bpm)	73.38	69.27 (66.36 – 77.41)	71.15 (47.68 – 67.03)	72.21 (69.15 – 75.10)	69.30 64.19 – 72.78)	0.90
cSDNN (ms)	184.64	172.65 (166.50 – 267.30)	197.20 (136.47 – 248.48)	179.40 (167.64 – 253.11)	172.41 (154.29 – 232.72)	0.98
SD1HR (ms)	6.07	8.63 (5.75 – 10.60)	9.52 (7.68 – 10.29)	7.63 (5.57 – 11.37)	8.72 (6.82 – 11.95)	0.46
SD2HR (ms)	73.84	77.59 (62.82 – 119.05)	77.29 (66.97 – 94.25)	79.11 (65.45 – 97.20)	76.88 (61.62 – 106.44)	1.0
SEHR	0.1312	0.1694 (0.1210 – 0.2078)	0.1715 (0.1472 – 0.1836)	0.1523 (0.1361 – 0.2037)	0.1788 (0.1468 – 0.2234)	0.53

Krushal wallis test with median (IQR) presented.

4.4.4.3 Heart rate variability measures in relation to ABE assessment tool

Most patients were either in group B (n = 20) or group E (n = 9). There were no significant differences in any heart rate variability measures amongst the three ABE groups.

4.4.4.4 Correlation between mean HR and sample entropy of HR

In health, studies have shown a negative linear correlation between the meanHR and SEHR. (236) In our study we found that this correlation was lost ($r = 0.005$, $p = 0.98$).

4.4.4.5 Respiratory rate variability measures in relation to the severity of airflow obstruction

Linear regression analysis found that there was a weak negative correlation between FEV1 and the mean RR (r = -0.394. p = 0.026) and SERR (r = -0.380, p = 0.032). This is illustrated in Figure 4-13 and 4-14. However, when corrected for age, gender and BMI, all of which can independently affect FEV1 in a stepwise linear regression model, FEV1 was no longer significantly associated with mean RR and SERR. The step-wise model results for each can be seen in Figure 4-15 and 4-16.

No significant associations were found with FEV1 and SDBB (r = 0.013, p =0.94), SD1RR (r = 0.130, p = 0.48) and SD2RR (r = 0.011, p = 0.95).

Figure 4-14 Correlation between mean RR and FEV1

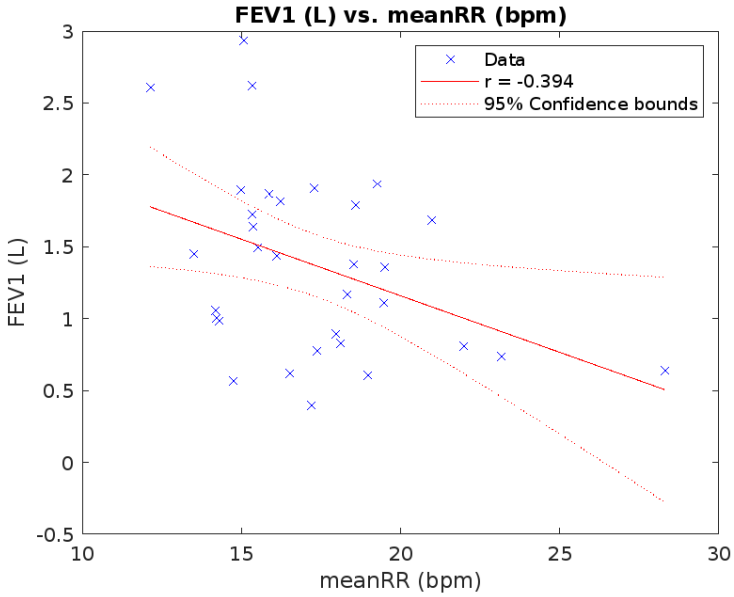


Figure 4-15 Correlation between SERR and FEV1

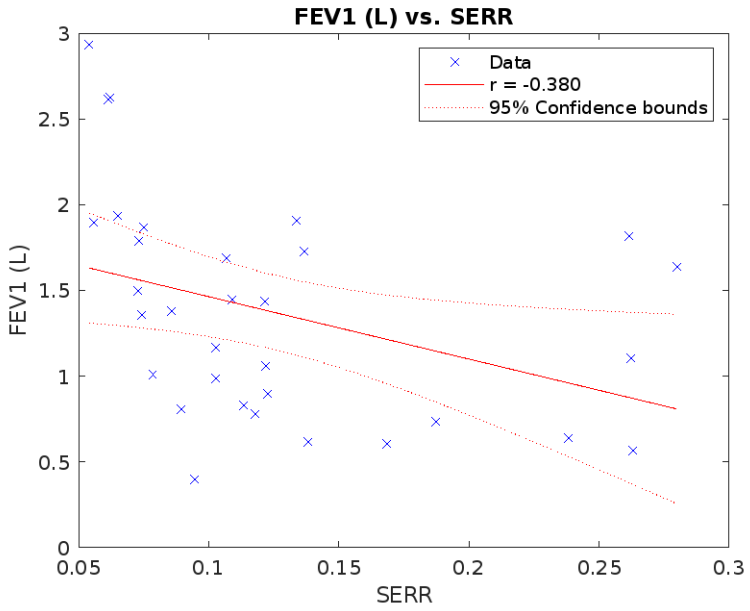


Figure 4-16 Step wise linear regression model with FEV1, BMI, age and gender for mean RR.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	20.024	1.266		15.814	<.001	17.438	22.610
	FEV1	-1.972	.840	-.394	-2.347	.026	-3.688	-.256
2	(Constant)	22.553	1.972		11.438	<.001	18.520	26.586
	FEV1	-1.353	.900	-.270	-1.504	.143	-3.194	.487
	BMI	-.124	.075	-.295	-1.643	.111	-.278	.030
3	(Constant)	21.278	4.447		4.785	<.001	12.170	30.387
	FEV1	-1.284	.939	-.256	-1.367	.182	-3.208	.640
	BMI	-.123	.077	-.293	-1.605	.120	-.280	.034
	Age	.017	.054	.055	.321	.751	-.093	.128
4	(Constant)	21.330	4.552		4.686	<.001	11.989	30.671
	FEV1	-1.248	1.013	-.249	-1.232	.229	-3.326	.831
	BMI	-.123	.078	-.294	-1.579	.126	-.283	.037
	Age	.015	.058	.048	.260	.797	-.105	.135
	Gender (0 = male, 1 = female)	.139	1.281	.021	.108	.915	-2.490	2.768

a. Dependent Variable: mean resp rate

Figure 4-17 Step wise linear regression model with FEV1, BMI, age and gender for SERR.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	.180	.027		6.779	<.001	.126	.235
	FEV1	-.040	.018	-.380	-2.254	.032	-.076	-.004
2	(Constant)	.194	.043		4.502	<.001	.106	.283
	FEV1	-.036	.020	-.348	-1.844	.075	-.077	.004
	BMI	-.001	.002	-.079	-.417	.680	-.004	.003
3	(Constant)	.061	.093		.656	.517	-.130	.253
	FEV1	-.029	.020	-.278	-1.476	.151	-.070	.011
	BMI	-.001	.002	-.068	-.369	.715	-.004	.003
	Age	.002	.001	.277	1.597	.121	-.001	.004
4	(Constant)	.066	.095		.698	.491	-.129	.262
	FEV1	-.025	.021	-.243	-1.202	.240	-.069	.018
	BMI	-.001	.002	-.072	-.386	.702	-.004	.003
	Age	.002	.001	.243	1.304	.203	-.001	.004
	Gender (0 = male, 1 = female)	.014	.027	.103	.525	.604	-.041	.069

a. Dependent Variable: SE resp rate

4.4.4.6 Respiratory rate variability measures in relation to symptom burden

There were no significant differences between respiratory rate variability measures and different severities of breathlessness as assessed by the mMRC score (Table 4-9). Linear regression analysis found no significant association with the CAT score and mean RR (r = 0.164, p = 0.38), SDBB (0.031, p = 0.87), SD1RR (0.081, p = 0.67), SD2RR (0.030, p = 0.87) or SERR (0.110, p = 0.56).

Table 4-9 Respiratory rate variability measures and different severities of breathlessness.

RRV measure	**mMRC 0 (n=2)**	**mMRC 1 (n=6)**	**mMRC 2 (n=6)**	**mMRC 3 (n=12)**	**mMRC 4 (n=6)**	**P value**
Mean RR (bpm)	17.68	15.71 (15.24 – 18.71)	18.45 (16.00 – 19.04)	15.13 (14.19 – 18.23)	17.66 (16.15 – 24.45)	0.28
SDBB (ms)	412.14	551.51 (385.90 – 883.45)	494.44 (426.33 – 547.04)	633.85 (451.03 – 764.75)	457.51 (294.12 – 646.14)	0.39
SD1RR (ms)	74.19	85.20 (78.14 – 142.67)	98.09 (78.68 – 110.75)	108.27 (87.71 – 132.02)	91.49 (61.12 – 100.63)	0.33
SD2RR (ms)	577.84	773.82 (540.55 – 1242.00)	688.93 (595.58 – 768.30)	889.66 (630.20 – 1073.23)	640.04 (411.45 – 907.67)	0.39
SERR	0.0745	0.1140 (0.0605 – 0.1261	0.1354 (0.0715 – 0.2661)	0.1057 (0.0804 – 0.1306)	0.1257 (0.0845 – 0.1998	0.66

Krushal Wallis test with median (IQR) presented.

4.4.4.7 Respiratory rate variability measures in relation to the ABE assessment tool.

Most patients were either in group B (n = 20) or group E (n = 10). There were no significant differences in any respiratory rate variability measures amongst the ABE groups.

4.4.4.8 Airflow variability in relation to the severity of airflow obstruction

Linear regression analysis found no significant association between FEV1 and α1 (r = 0.294, p = 0.12), α2 (r = 0.056 p = 0.77) and α3 (r = 0.201, p = 0.30).

4.4.4.9 Airflow variability measures in relation to symptom burden

A one-way analysis of variance (ANOVA) showed no significant differences between any of the airflow variability measures and different severities of breathlessness as assessed by the mMRC score. Linear regression found no significant association with the CAT score and α1 (r = 0.092, p = 0.64), α2 (r = 0.329, p = 0.09) and α3 (0.364, p = 0.06).

4.4.4.10 Airflow variability measures in relation to the ABE assessment tool.

There were no significant differences in any airflow variability measures amongst the three ABE groups.

4.4.5 Physiological signal variability measures in the exacerbating COPD group

The first nocturnal recording (within 48 hours of admission) was used to assess whether there were any associations with the admission NEWS2 score, CRP, ROME severity classification and length of stay.

Admission NEWS2 score

The median (IQR) admission NEWS2 score was 5 (3 – 6). There were no significant correlations between the NEWS2 score and any of the physiological signal variability measures. This is illustrated in Table 4-10.

Table 4-10 Correlation between the admission NEWS2 score and the physiological signal variability measures.

Variability measurement	Pearson's Correlation Coefficient	P value
Heart Rate measurements		
Mean HR	-0.326	0.39
cSDNN	-0.478	0.19
SD1HR	-0.312	0.41
SD2HR	-0.158	0.69
SEHR	-0.328	0.39
Respiratory Rate measurements		
Mean RR	-0.60	0.81
SDBB	0.036	0.89
SD1RR	0.081	0.75
SD2RR	0.035	0.89
SERR	0.007	0.98
Airflow measurements		
Alpha 1	-0.166	0.61
Alpha 2	-0.341	0.34
Alpha 3	-0.008	0.98

Admission CRP

The mean (SD) admission CRP was 54 ± 66. There was a significant negative correlation between alpha1 (airflow) and the CRP (correlation coefficient -0.58, p = 0.049). No other significant correlations were found amongst any of the other physiological variability measures.

ROME Proposal severity classification

Binomial logistic regression was not performed for heart rate measurements or airflow measurements given the sample size was very small (n=9). Binomial logistic regression to ascertain the effects of mean RR, SDBB, SD1RR, SD2RR and SERR on the likelihood of having a mild or moderate exacerbation as per the ROME proposal was not statistically significant ($\chi 2 = 1.929$ (5), p = 0.86).

Length of stay

The median length of stay was 5 (3 – 7) days. There was no correlation between any of the physiological variability analysis measures (HR, RR and airflow) with the length of stay. Although there was a trend towards a positive correlation with mean RR (correlation coefficient = 0.432, p = 0.07) and negative correlations with SDBB (correlation coefficient = -0.403, p = 0.097) and SD2RR (correlation coefficient -0.403, p = 0.097).

4.4.6 Differences in physiological signal variability measures at admission, discharge and post discharge in the exacerbating group

Three participants stopped using AcuPebble RE100 after their first night, two participants did not use AcuPebble RE100 the night prior to discharge meaning no data was available, one participant was only admitted for one day, and one participant, while admitted for four days, due to data collection windows for admission and discharge being 48 hours and due to artefact, only the reading 48 hours into admission was available. Therefore, 11/18 nocturnal discharge recordings were available. Most recordings were taken from the night prior to discharge, with 2/11 being from 48 hours prior to discharge to maximise data capture. From the 11 recordings due to artefact, 6/11 HR, 10/11 RR and 8/11 airflow recordings were available for analysis. Table 4-11 illustrates the findings. As the majority of the measures were not normally distributed, the Wilcoxon Signed-Rank Test was used, and data presented as median (IQR). No significant differences were found in any of the measures.

Table 4-11 Differences in measures at admission and discharge.

Physiological variability measure	Admission	Discharge	p-value*
Heart Rate (HR) measures			
Mean HR (bpm)	74.22 (67.42 – 82.31)	82.62 (75.19 – 93.49)	0.5
cSDNN (ms)	268.41 (206.67 – 314.90	279.86 (220.47 – 389.75)	0.35
SD1HR (ms)	12.06 (7.76 – 14.51)	11.53 (9.70 – 13.11)	0.35
SD2HR (ms)	90.18 (78.62 – 130.15)	95.13 (82.48 – 114.81)	0.23
SEHR	0.1258 (0.1044 – 0.1568)	0.1281 (0.1032 – 0.1550)	0.89
Respiratory Rate measures (RR)			
Mean RR (bpm)	18.58 (15.27 – 20.50)	16.63 (14.42 – 21.04)	0.58
SDBB (ms)	628.68 (514.90 – 1126.30)	732.29 (620.18 – 1158.03)	0.80
SD1RR (ms)	133.61 (95.52 – 168.53)	126.35 (87.74 – 166.60)	0.88
SD2RR (ms)	875.93 (722.42 – 1584.36)	1027.97 (872.62 – 1627.45)	0.80
SERR	0.1378 (0.0982 – 0.1916)	0.1193 (0.0979 – 0.1697)	0.06
Airflow analysis (detrended fluctuation analysis)			
Alpha 1	1.6294 (1.6055 – 1.6452)	1.6215 (1.6095 – 1.6580)	0.92
Alpha 2	0.2968 (0.2779 – 0.3110)	0.2932 (0.2826 – 0.3136)	0.35
Alpha 3	0.5000 (0.4676 – 0.5578)	0.5265 (0.4562 – 0.6167)	0.46

Data presented as median (IQR). Wilcoxon signed-rank test used.

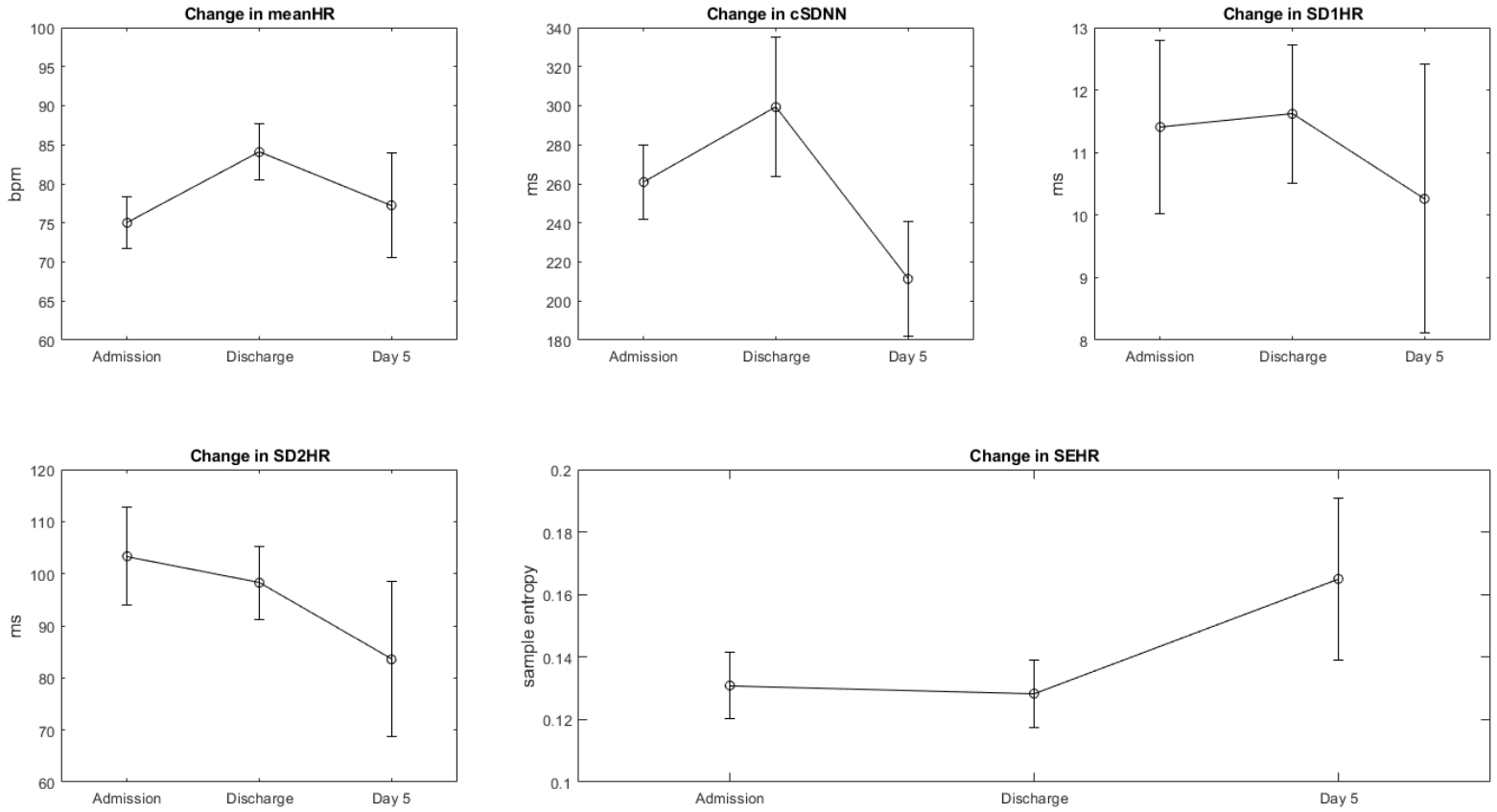
Post discharge day 4-5 nocturnal data was available in nine participants, however due to artefact, data was available for 6/9 HR, 8/9 RR and 7/9 airflow recordings. Given the small numbers involved, statistical analysis with Friedman's test was not computed. At five days post discharge, the mean HR was largely unchanged, but the variability measures (cSDNN, SD1HR and SD2HR) trended downwards, while sample entropy of HR increased. While

the mean RR was also largely unchanged, the other variability measures all decreased at five days post discharge compared to admission values. This is illustrated in Figures 4-18 and 4-19. Airflow measures alpha 1 and alpha 2 decreased from admission to post discharge, while alpha 3 increased. This is illustrated in Figure 4-20.

MSE analysis of the HR time-series, showed no difference between the admission and discharge sample entropy at all scales, but the sample entropy was increased at five days post discharge at all scales. This is illustrated in Figure 4-21.

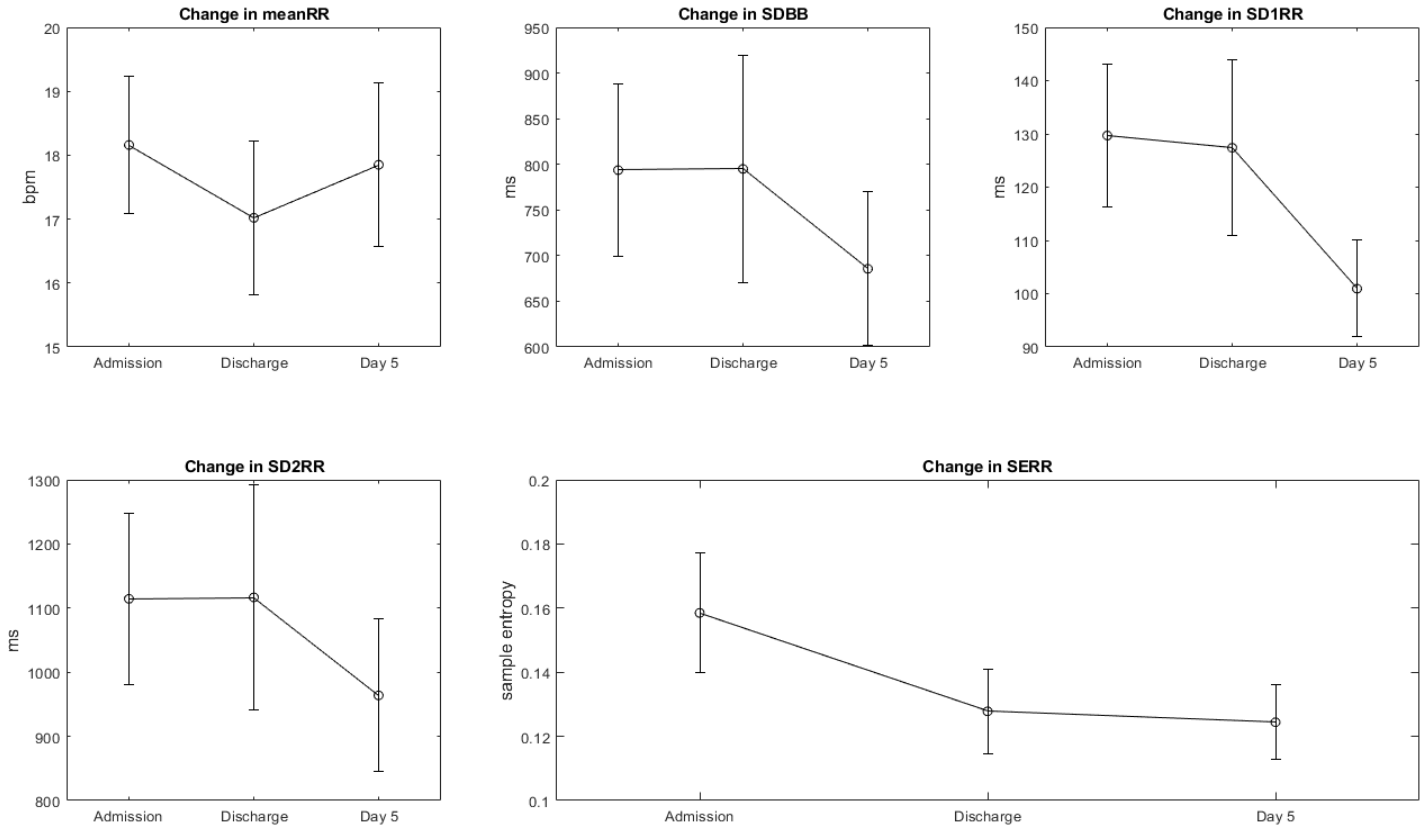
MSE analysis of the RR time-series, showed no difference between the admission and discharge sample entropy at all scales, but the sample entropy at five days post discharge seemed to be lower at higher scales. This is illustrated in Figure 4-22.

Figure 4-18 Heart rate variability measures at admission, discharge and 5-days post discharge



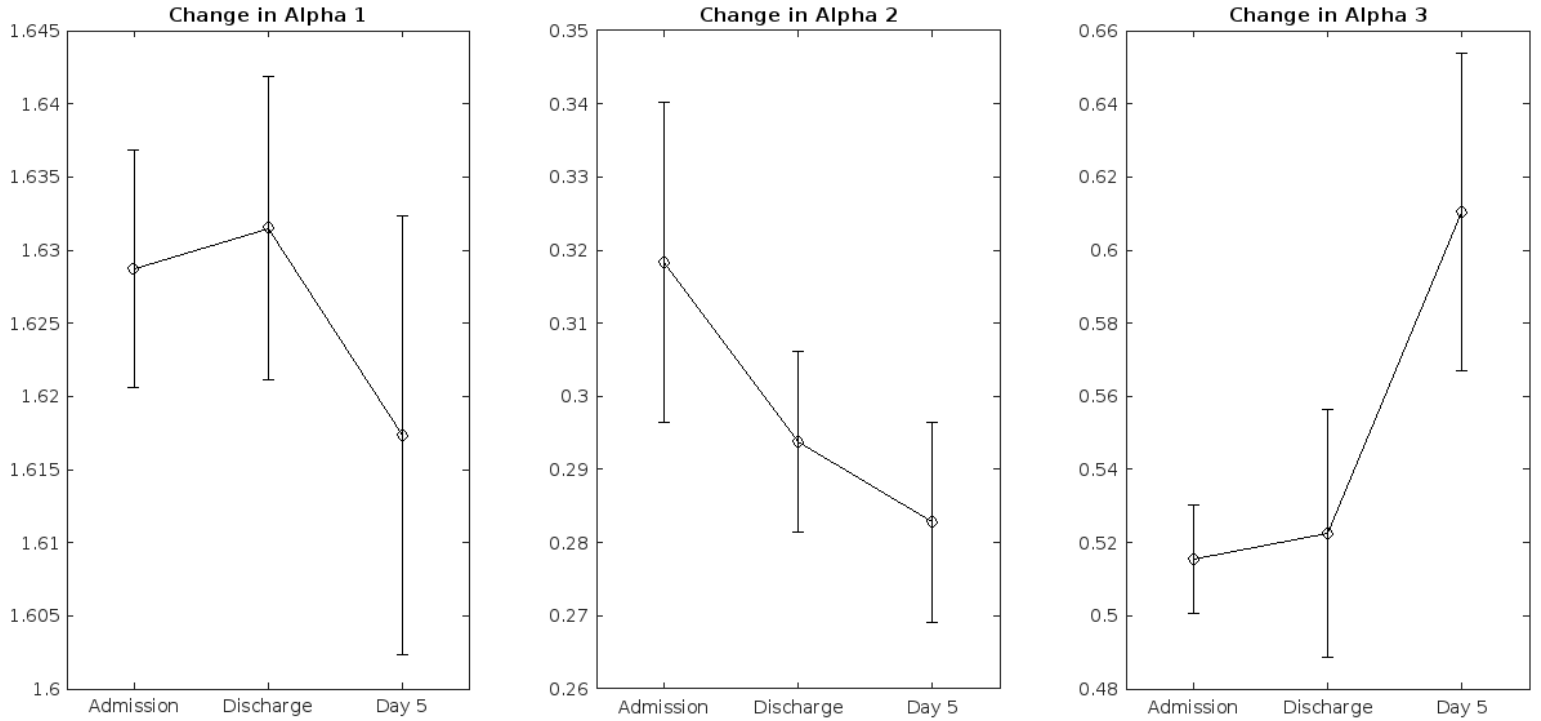
Circles represent the mean value and error bars represent the standard error.

Figure 4-19 Respiratory rate variability measures at admission, discharge and 5-days post discharge.



Circles represent the mean value and error bars represent the standard error.

Figure 4-20 Airflow measures at admission, discharge and 5-days post discharge.



Circles represent the mean value and error bars represent the standard error.

Figure 4-21 MSE analysis of HR time-series at admission, discharge and 5-days post discharge.

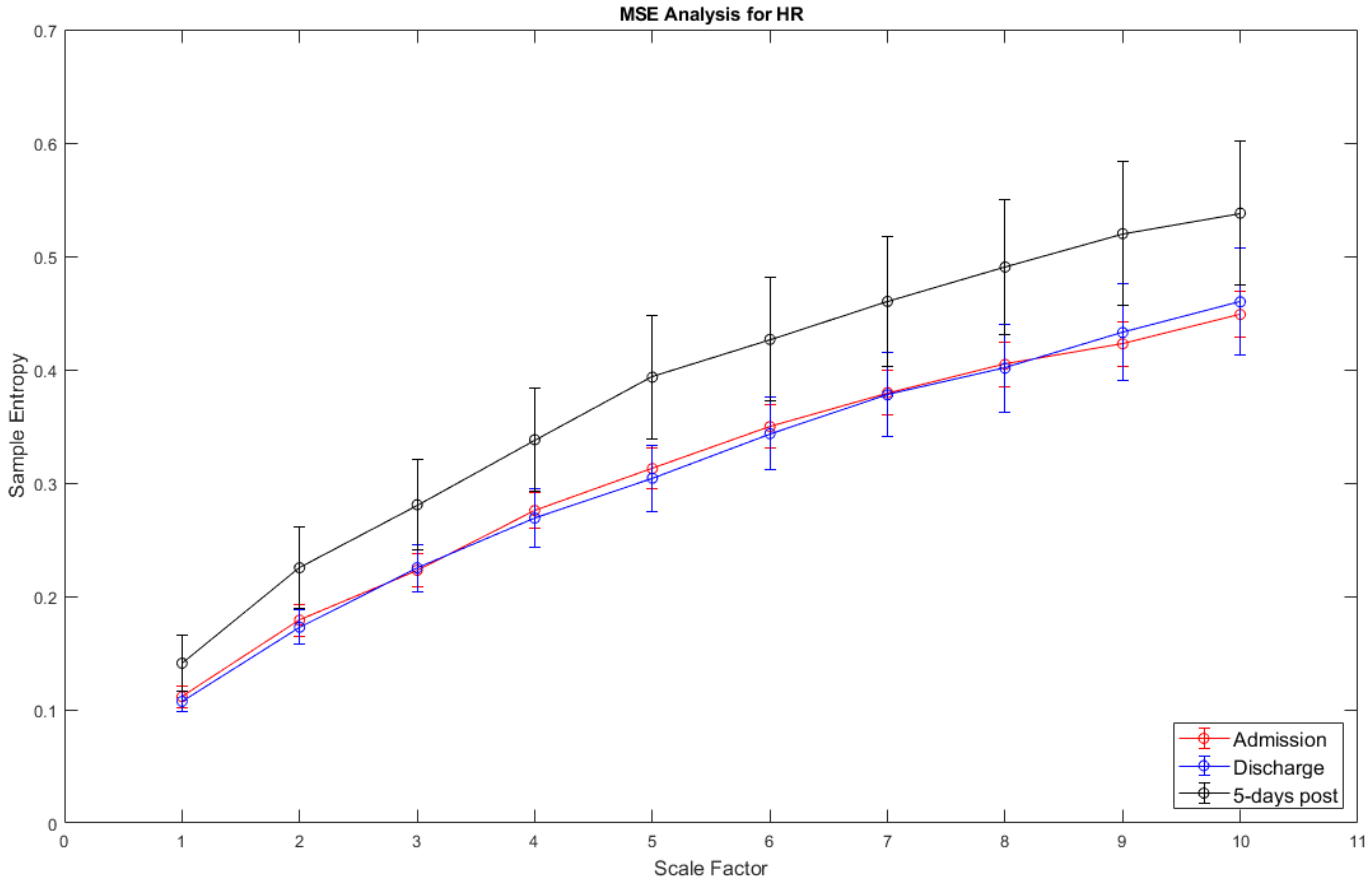
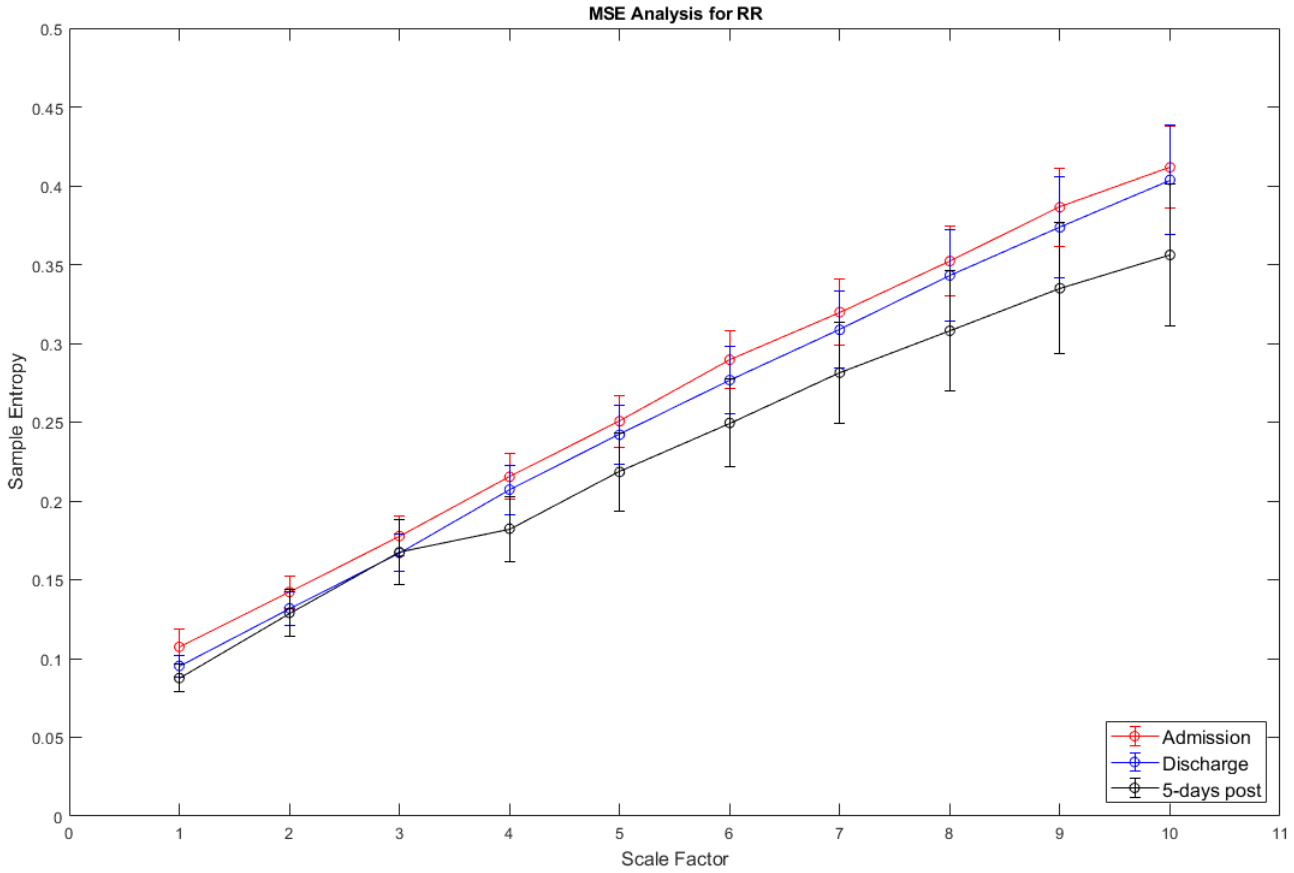


Figure 4-22 MSE analysis of RR time-series at admission, discharge and 5-days post discharge.

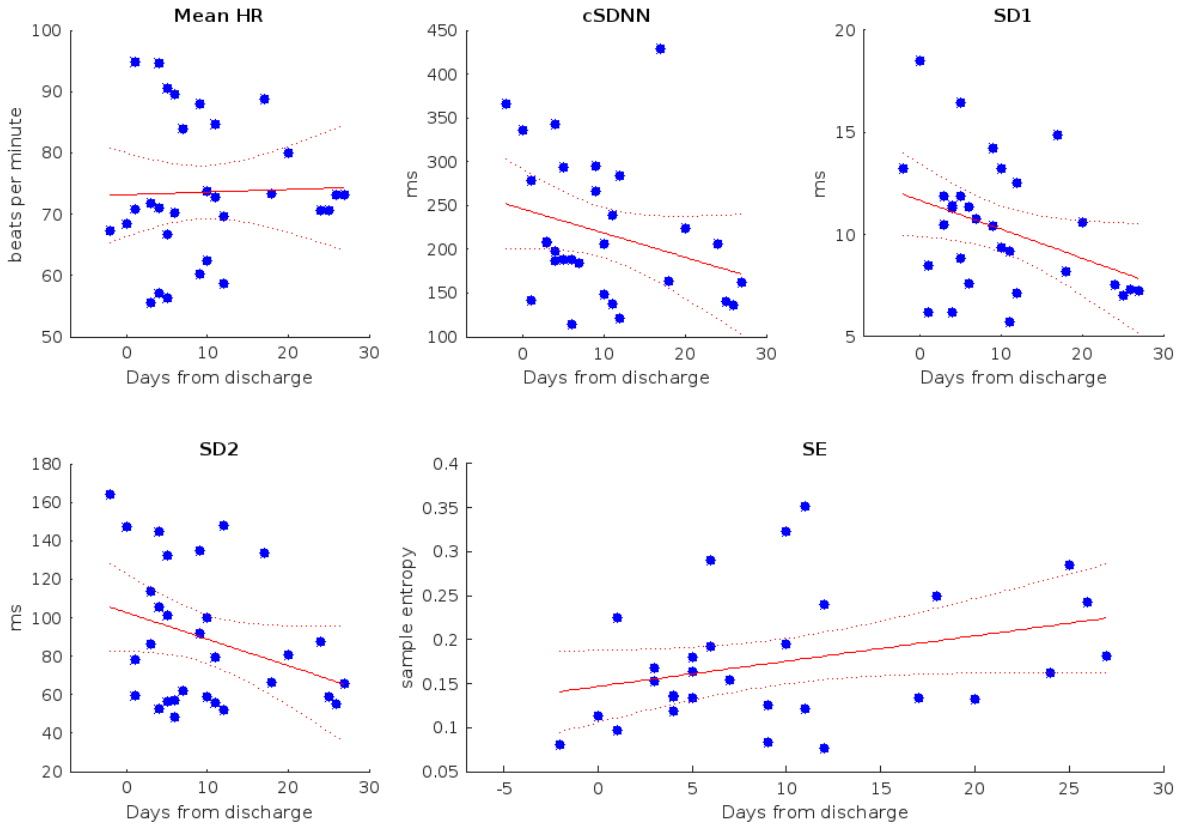


Three participants used the device for at least 10 days post discharge, with one participant using it for 26 days. Figures 4-23 and 4-24 illustrate the HR and RR variability measures respectively, from admission, at the point of discharge (day 0) and each subsequent day following discharge. There was no change in the mean HR following discharge. Several HR variability measures (cSDNN, SD1HR and SD2HR) showed decreased variability following discharge, while sample entropy of HR increased following discharge. Linear regression showed no significant differences in these trends.

There was a trend towards an increasing meanRR following discharge, although there was significant variability in the data. SDBB and SD2RR showed no change following discharge, while SD1RR had a decreasing trend. Sample entropy of RR significantly decreased following discharge ($R^2 = 0.297$, $p < 0.001$).

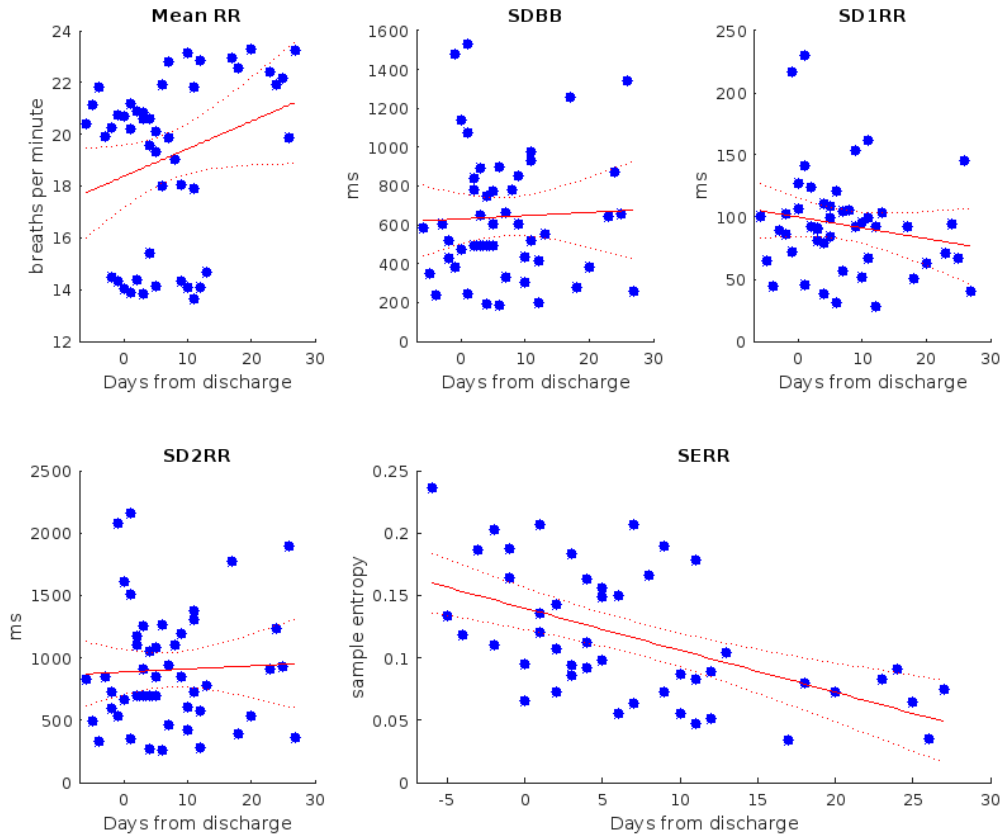
There was a trend towards increasing alpha 1 ($R^2 = 0.121$, $P = 0.017$) and alpha 2 values following discharge, but alpha 3 showed no obvious change in pattern. This is illustrated in Figure 4-25.

Figure 4-23 Heart rate variability measures from admission to post discharge.



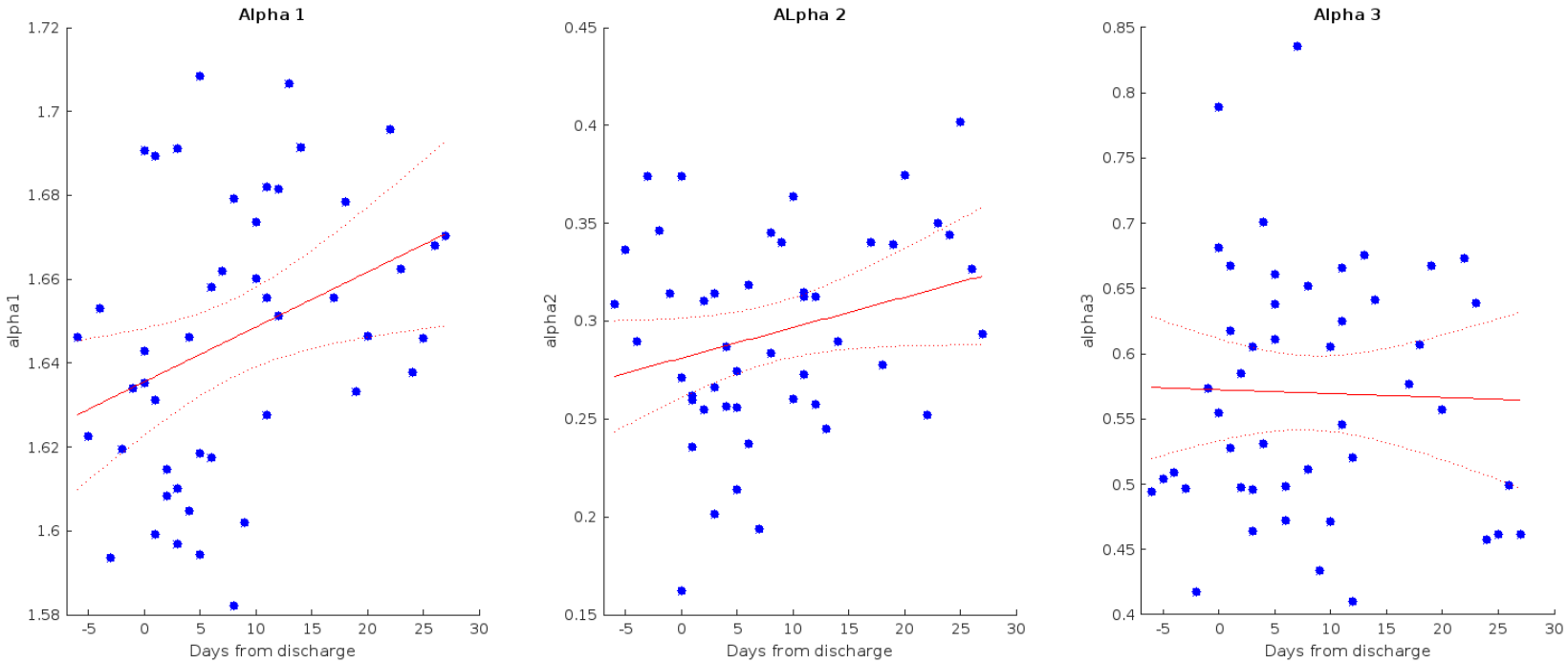
Data taken from three patients. The red line indicates the linear regression fit with confidence intervals. None were significant

Figure 4-24 Respiratory rate variability measures from admission to post discharge.



Data taken from three patients. The red line indicates the linear regression fit with confidence intervals. SERR had an R^2 value of 0.297, $p<0.001$.

Figure 4-25 Airflow variability measures from admission to post discharge.

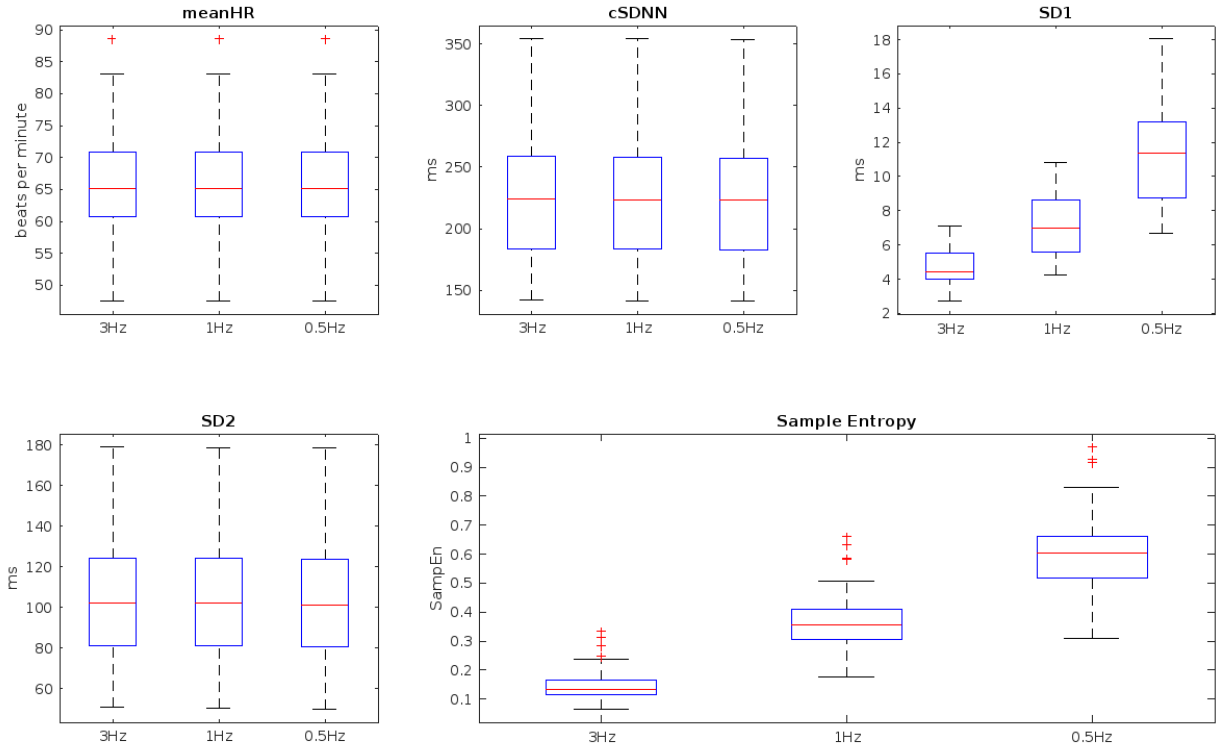


Data taken from three patients. The red line indicates the linear regression fit with confidence intervals. Alpha 1 had an R^2 value of 0.121, $p<0.017$. Nil other significant differences seen.

4.4.7 HR variability measures from multi-channel polygraphy in non-COPD cohort

Overnight HR data from the multi-channel polygraphy was available for 48 non-COPD participants, but 2 participants had a high degree of artefact and therefore 46 recordings were analysed. Figure 4-26 illustrates the variability measures at different resolutions (3Hz, 1Hz and 0.5Hz). The meanHR, cSDNN and SD2 measures of variability were similar at the different resolutions. However, SD1 and SEHR measures progressively increased at lower resolutions (i.e., when we 'zoomed' out of the data, SD1HR and SEHR increased in value).

Figure 4-26 Box-plots for each variability measurement at different resolutions from the multi-channel polysomnography.



Boxplot representing the median and IQR. The whiskers represent the minimum and maximum values (bar any outliers). Outliers represented by the red cross are values which lie above Q3 + (1.5 x IQR).

4.4.8 Comparing HR variability measures from AcuPebble SA100 and the multi-channel polygraphy in the non-COPD cohort.

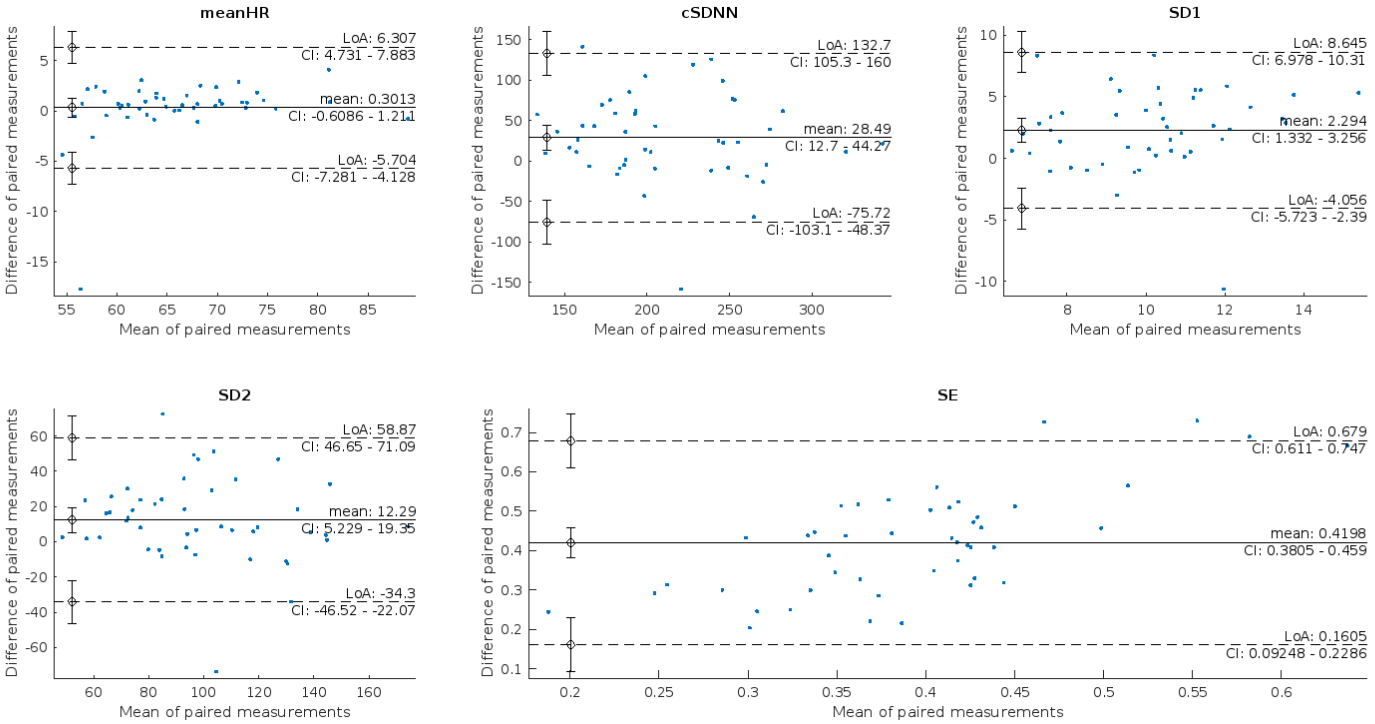
Heart rate variability measures calculated from the multi-channel polygraphy recordings significantly varied from HR measures calculated from AcuPebble SA100 at the same resolution (0.5Hz), with very low intraclass correlation coefficients (ICC) and a high degree of bias in the Bland Altmann Plots. The exception to this was the mean HR which was similar for both devices (ICC 0.918). This is shown in Table 4-12. Figure 4-27 illustrates the Bland-Altman plots for each of these variables, showing a high mean difference (and therefore bias) for all measurements except the mean HR where the mean difference and bias was 0.30 (-0.61 – 1.21) beats per minute.

Table 4-12 HR variability measurements from AcuPebble SA100 and the overnight multi-channel polygraphy at the same resolution.

Variability measure	AcuPebble HR data	Multi-channel polygraphy data	ICC
Mean HR (bpm)	64.95 (60.66 – 69.84)	65.19 (60.67 – 70.86)	0.918
cSDNN (ms)	188.35 (146.70 – 243.92)	223.00 (181.71 – 259.57)	0.479
SD1 (ms)	9.04 (7.07 – 10.44)	11.39 (8.72 – 13.22)	0.160
SD2 (ms)	87.27 (65.56 – 117.03)	101.37 (80.27 – 123.83)	0.653
SE	0.1892 (0.1331 – 0.2309)	0.6039 (0.5158 – 0.6644)	0.027

As most of the data was non-parametric the median (IQR) has been shown the intraclass correlation coefficient (ICC) was calculated using a two-way mixed method with absolute agreement.

Figure 4-27 Bland-Altman plot comparing heart rate variability measured by AcuPebble SA100 vs. multi-channel polygraphy.



4.4.9 Acceptability of AcuPebble RE100 in the stable COPD population

Usability feedback was obtained from 24/33 (73%) of the participants. The majority (16/24) found attaching the sensory very easy with no participant finding the sensor very difficult or difficult to attach. While many participants (14/24) found the sensor very easy to pair with the mobile phone application, 3/24 (13%) found this difficult. Most participants (17/24) found the sensor comfortable to wear with 60% finding it more comfortable than a plaster. This is illustrated in Figure 4-28a and 4-28b. In the majority (20/24) the sensor stayed in place for the duration of the night, and only one participant experienced side effects of red skin over the site. General issues noted by participants included problems with charging the sensor and delay in uploading the data to the cloud. While some patients found the sensor uncomfortable and tedious for four weeks, several thanked us for ‘letting them take part’, found the study easy, well presented and straightforward.

Figure 4-28 Attachment and comfort of sensor

Figure 4-28a: Ease of attaching the sensor and application.

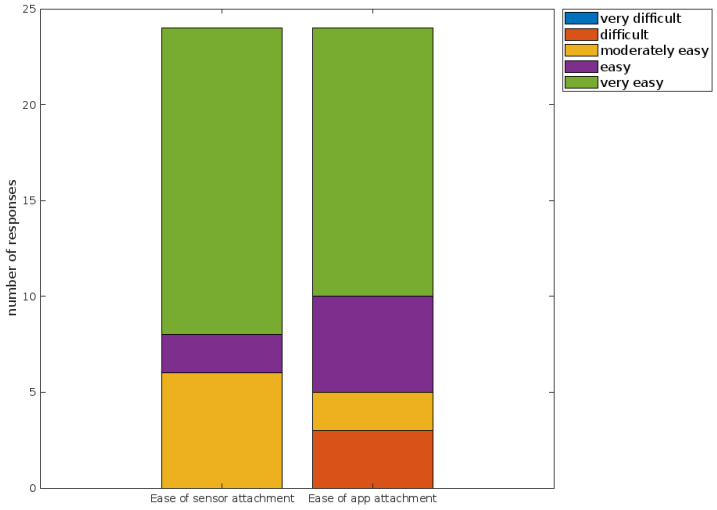
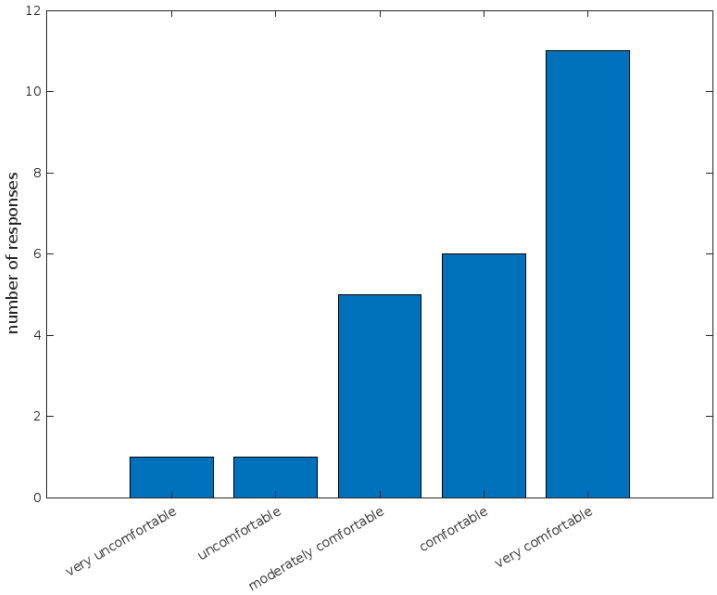


Figure 4-28b: Comfort level of the sensor



4.4.10 Acceptability of AcuPebble RE100 in a group of COPD patients undergoing an exacerbation

Usability feedback was obtained from 8/18 participants. All participants found it at least moderately easy to put the sensor on and attach the app with 38% finding it very easy. 75% of participants found the sensor comfortable with only one participant finding it uncomfortable. However, it is worth noting that 4/18 participants only managed one recording due to finding the sensor uncomfortable or the sensor falling off. None of these four filled out the usability questionnaire. Only one participant developed a red rash around the site of the device, but this disappeared through the day and the participant was able to carry on. There were four general comments provided by participants which are outlined below:

> *"felt like I was choking, very uncomfortable"*
>
> *"excellent machine. I wished I had one"*
>
> *"not too good at technical things"*
>
> *"psychological.. having something on my neck scared me. The doctor was helpful and professional"*

The inpatient diaries provided to participants were incomplete with no reliable and usable data.

4.5 Discussion

The feasibility of this study was tested using the ACCEPT model. (237)

1) Sample size and participants
    a. 52% of eligible participants agreed to take part in the study
    b. Only one participant in the stable group used the device for the entire duration of the study (30 nights). Median (IQR) use was 18 nights (10 – 26).
    c. There was a high attrition rate amongst the exacerbating group with admission data available for 78% of participants, discharge data for 61% participants, day five post discharge in 50% and only 17% using the device for at least 10 days post discharge.
2) Wearable Technology
    a. More than 65% of participants in the stable group found the sensor easy to use and comfortable to wear.
    b. 75% of participants undergoing an exacerbation found the sensor comfortable to wear but importantly 22% only managed one nocturnal recording due to discomfort.
    c. Heart rate and airflow recordings had greater noise interference and artefact compared to the respiratory rate recordings.
3) Outcomes
    a. There were significant differences in physiological signal variability measures between stable COPD participants and the exacerbating group.

b. HR variability measures derived from AcuPebble devices significantly differed from measures derived from the multi-channel polygraphy. This may limit their reliability in distinguishing stable COPD patients from a non-COPD population. However, if the same device is used, trend differences, as opposed to actual values, can be used as a differentiator. Furthermore, MSE analysis, which is more robust and not impacted by resolution did suggest a difference.
c. Multi-scale entropy (MSE) analysis of the heart rate time-series suggested that participants undergoing an exacerbation of COPD have a significantly lower sample entropy compared to the stable COPD group and non-COPD patients, regardless of scale.
d. MSE analysis of the respiratory rate time-series suggested that participants undergoing an exacerbation of COPD have a significantly higher sample entropy compared to the stable group and non-COPD group regardless of scale. This difference is more apparent at larger scales.
e. DFA analysis of airflow variability showed two-cross over points; and suggested that at intermediate scales, stable COPD participants had less anti-correlation compared to non-COPD participants.
f. DFA analysis of airflow variability suggested that at longer scales, participants undergoing an exacerbation of COPD had a

significantly lower α3 value compared to the stable population and this was suggestive of random fluctuation.

g. No significant differences in any variability measures were found for different phenotypes of stable COPD.
h. There were limited significant correlations with any physiological signal variability measure and currently measured admission severity characteristics.
i. The resolution of time-series measurements impact variability analysis and are an important consideration for future work.

4.5.1 Baseline characteristics

Compared to the stable group, participants undergoing an exacerbation had no significant differences in age, gender, smoking history, and medical comorbidities. As expected, they had significantly worse lung function with a reduced FEV1, FVC and TLCO and a higher CAT symptom score. A greater proportion of exacerbating patients were in GOLD category E compared to the stable group. This can be explained by the fact that the greatest predictor of a future exacerbation is having an exacerbation history, (36) meaning participants admitted for a COPD exacerbation are likely to have had one previously, thus putting them in a higher GOLD COPD category. This also explained why fewer exacerbating participants were on a LAMA/LABA combination inhaler on admission compared to the stable group. Therefore, participants undergoing a COPD exacerbation, as expected, represented a more severe COPD cohort.

Admitted patients were tachypnoeic, tachycardic and hypoxic with a median NEWS2 score of 5 (3 – 6) and had a median length of stay of 5 days (3 – 7). This is slightly lower than a previous large cross-sectional audit from 13 European counties that found the median length of stay was 7 days (4 – 11). (238) This is probably because this study excluded patients requiring non-invasive ventilation, who represent the sickest patients and are likely to be in hospital for a prolonged period of time, thus skewing the results.

4.5.2 Usability and acceptability of AcuPebble RE100

4.5.2.1 Stable group

Only one participant used the device for the entire duration of the study (30 nights). However, most patients used it for 60% (median 18 nights (10 – 26)). One participant used it for only 2 nights. This participant had several issues with the mobile phone signal and upload of daily content and so returned the device early. Most participants used the device for at least 6 hours overnight (median 8.3 hours (6.8 – 9.8)), which is likely to have adequately captured the various stages of sleep. The HR recordings and airflow data from AcuPebble RE100 had greater noise interference / artefact than the RR recordings, leading to more aberrant and missing data. Therefore only 65% (338/519) of the 6-hour HR recordings and 66% (345/519) of the airflow recordings were adequate for analysis compared to 95% (492/519) of the 6-hour RR recordings. This suggests that if HR or airflow fluctuations are needed to create a future exacerbation prediction algorithm, a longer device recording period may be needed compared to RR, to account for potentially higher level of missing data.

Given the limited data currently available on nocturnal physiological variability analysis, there is no gold standard duration of analysis recommended for COPD patients. Bland Altman plots comparing mean hourly to 6-hourly data analysis showed low mean differences and less bias for meanHR, SD1HR, SEHR, meanRR and SERR. The other measures were skewed with high bias. Some of this may be explained in part by the effect of thermoregulation. Thermoregulation is thought to affect long term fluctuations in heart rate variability and studies have shown that cooler temperatures are associated

with increased SDNN and SD2HR (markers of longer-term variability). (231, 239, 240) This may mean that heart rate variability measures for the 1st hour of sleep are significantly different to the 6th hour of sleep, given our body temperature cools overnight, giving a skewed overall representation, that is different from the total 6-hour recording which in-corporates longer term fluctuations. Moreover, it is well recognised that longer term analysis allows a better representation of the overall response of a system. (231) Given this, I have established that a 6-hour analysis timeframe is likely to be more accurate than hourly measurements, and that this comparable across both HR and RR measures.

Usability feedback from stable participants, found that the majority found the device comfortable, had minimal side effects and found attaching the sensor and app easy. As expected, some participants struggled with this and future work should focus on detailing these struggles, so that future versions of the wearable and application can be made simpler. There were some comments regarding charging the sensor, given the short battery life and data upload. Both these problems can be fixed in future iterations of the product.

4.5.2.2 Exacerbating group

Out of 23 consented participants undergoing an exacerbation, admission data was only available for 18 (78%) participants. Discharge data was available for 11/18 (61%) participants. Three participants (17%) stopped using AcuPebble RE100 after the first night due to discomfort, while two didn't use it the night prior to discharge. Day five post discharge data was available in 9/18 (50%) of participants, while three participants used the device for at least 10 days post-discharge. This suggests a high attrition rate amongst our participants who

have been admitted with COPD. This is not dissimilar to a recent study, in which participants had to wear a vest-like wearable device post COPD exacerbation for six-weeks and 29/50 (58%) completed the follow-up period. (241)

However, this is lower than studies investigating pulmonary rehabilitation (PR) and self-management post COPD exacerbation, where a systematic review of 43 studies found that the drop-out rate was less than 30% for 93% of the included studies. (242) This difference is likely to be explained by the fact that wearable technology adoption amongst older adults is still low. (243, 244) Furthermore, PR and self-management strategies have been around for considerably longer with greater publicity, thus perhaps participants are more likely to engage. Therefore, further work needs to be done, in motivating older participants to use wearables for a prolonged period. This is important as future devices that may be used to predict an upcoming exacerbation will need to be used for a long duration. It is likely that for this strategy to work, partnerships with respected lung charities such Asthma and Lung UK will need to be made to help publicise the benefits of future wearables.

Usability feedback from the device was completed by 8/18 (44%). All participants found the device and app moderately easy with 75% of participants finding the actual sensor comfortable. However, 4/18 participants (22%) only managed one recording due to finding the sensor uncomfortable or falling off due to increased perspiration secondary to being unwell.

4.5.3 Heart rate variability analysis

The heart rate (HR) and rhythm are continuously and dynamically regulated by the autonomic nervous system (ANS). The parasympathetic nervous system (PNS) slows the HR down almost immediately and thus regulates the HR on a beat-by-beat basis, accounting for the short-term variability. The sympathetic nervous system (SNS) releases catecholamines and increases the HR, with a slower onset, accounting for longer-term variability. It is important to note that the PNS and SNS do not merely have opposite effects but a complex interplay with often overlapping and different time frequencies of action. (245) Moreover, the ANS is not the only regulatory mechanism of heart rate variability with thermoregulation, chemoreceptors and the circadian rhythm all playing a role. (231) This complex interplay can be somewhat captured by analysing different measures of HR variability and complexity.

Heart rate variability is defined as the fluctuation in the interval between successive heartbeats. (231) It thereby follows that the gold standard measurement of heart rate variability is through an ECG recording that can capture each successive R-R interval. However, for prolonged recordings, this is cumbersome for patients. The R-R interval data for this study was derived from the pulse rate (integer HR) and therefore may be less accurate than direct ECG measurements.

4.5.3.1 Heart rate variability between stable COPD participants and the non-COPD group.

Our data showed that the mean HR calculated with AcuPebble RE100 was significantly higher in patients with stable COPD compared to the historical non-COPD cohort (71.04 (64.55 – 75.10) vs. 65.48 (60.83 – 70.03), p = 0.002).

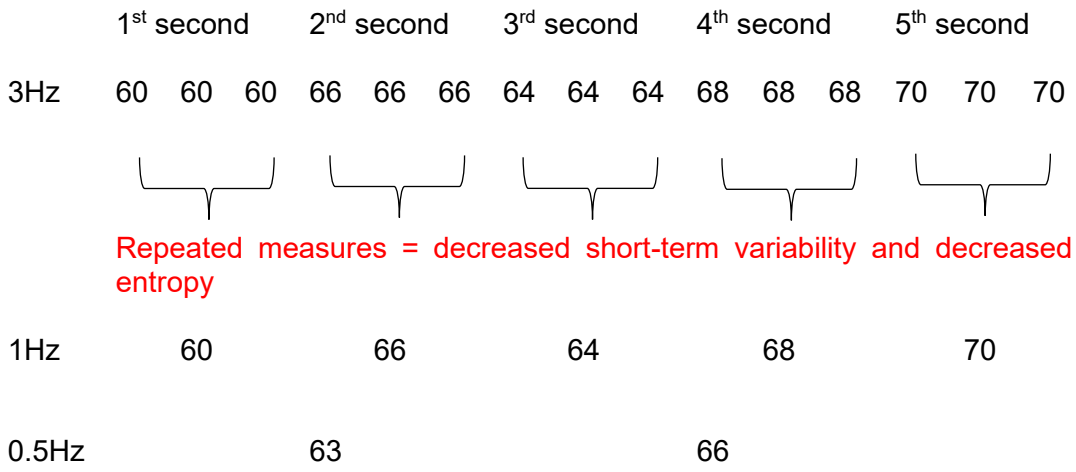
For all other variability measures (cSDNN, SD1HR, SD2HR and SEHR), there was no significant difference found between stable COPD participants and non-COPD participants.

However, when we investigated the non-COPD participant data comparing AcuPebble SA100 and the pulse oximetry data from the multi-channel polygraphy, at the same resolution (0.5Hz), there was poor correlation in the variability measurements despite good correlation for the mean HR from each device (ICC 0.918). This suggests, that AcuPebble SA100 may not accurately reflect the underlying variability around the mean value. This is likely to be due to how each device measures the pulse rate. AcuPebble SA100 and RE100 are both acoustic devices, placed at the neck, which detect the first and second heart sounds which are then processed to get the average heart rate (measured every 2 seconds). Moreover, there are multiple layers of filters to remove artefact (e.g., noise and breathing sounds). However, hidden in this may be the subtle variation (appearing as noise) around the mean HR which is missed or mistaken to be artefact. This leads to increased regularity, less randomness and thus decreased supposed variability and complexity. This may explain why the variability measures derived from non-COPD AcuPebble SA100 recordings were lower than those derived from the polygraphy (Table 4-12). The multi-channel polygraphy pulse oximeter identifies the pulse via photoplethysmography (PPG) which is a well-established technique and so perhaps more accurate. However, a recent review showed that while pulse rate variability (measured via PPG) has been largely used in the literature as a validated surrogate for heart rate variability (measured by ECG), the

relationship is still not completely clear, especially in an aged or unhealthy population. (246)

This work has also shown that varying resolution of the heart rate time series can impact certain variability measurements. The pulse oximetry HR recordings had an initial resolution recording of 3Hz, meaning three HR recordings were noted every second. However, the mean HR for this patient population was just over 60 beats per minute, giving an R-R interval of roughly 1s. Thus, changes in R-R interval can only really be appreciated in recordings that have a resolution of 1Hz or less. At a resolution of 3Hz, there will be several repeated HR measurements (as the three samples for the first second will have the same HR and same R-R interval) meaning a false sense of periodicity will ensue. This will give the impression of increased regularity and less randomness. When the resolution is decreased (by averaging adjacent values), a more realistic impression of the 'true' HR and variability can be seen. This idea is illustrated in Figure 4-29.

Figure 4-29 The impact of resolution on variability measurements



Our data showed that for the mean HR, cSDNN and SD2HR decreasing the resolution had little bearing on the actual values, while at decreasing resolution, the values for SD1HR and SEHR increased. This can be explained by the fact the cSDNN is a global measure of variability and SD2HR a measure of longer-term variability, thus less affected by short-term periodicity. However, SD1HR is representative of short-term (beat-to-beat) variability, therefore, increased regularity (at higher resolution) will give the impression of less variability. Decreasing the resolution and getting a more accurate data picture will show the increased short-term variability that truly exists. Sample entropy is a measure of complexity and determines the degree of randomness vs. periodicity. Therefore, falsely having repeated measures will decrease the entropy.

Multi-scale entropy (MSE) analysis of heart rate recordings from AcuPebble devices increased in both stable COPD patients and non-COPD patients with increasing scale, confirming that the HR time-series recorded was a complex physiological signal. Moreover, MSE analysis showed a significant reduction in heart rate sample entropy, irrespective of scale, in the stable COPD

participants compared to non-COPD, (F_{group} (1,19) = 5.61; p = 0.018). Multiscale entropy can further define the richness / complexity of a time-series by taking into account the multiple time scales that exist in physiological systems. By course graining / zooming out from the data, you can look at the complexity at varying scales, a concept that is otherwise ignored by conventional entropy calculations. (247, 248) Previous work by Norris et al looked at HR MSE in 3154 patients in intensive care. The HR was measured by conventional hospital monitors giving integer (pulse rate) values at varying frequencies ranging from 0.25Hz (4 samples / second) to 1hz. They found that MSE was robust to variations in data resolution, density and missing data. (249) This suggests that AcuPebble RE100 derived HR MSE is likely to be accurate.

Previous work investigating heart rate variability measures in the COPD population has largely focused on time-domain and power measures. Several studies have shown that daytime SDNN (with recordings of varying durations) is significantly reduced in COPD patients compared to healthy controls. (250-254) Moreover, a recent meta-analysis of seven studies showed a standardised mean difference (95%CI) of 1.26 (0.63 – 1.89) between patients with COPD and age and/or sex-matched controls, with lower SDNN values consistently reported in patients with COPD. However, all of these studies utilised 24-hour recordings. (255) This systematic review identified only one study from 22 that looked at nocturnal HR, which showed a median SDNN of 83ms (65 – 99) in the healthy cohort vs. 80ms (66 – 95ms) in the COPD population. (256) This is interesting as it perhaps suggests that while daytime or 24-hour variability is decreased in the COPD population, isolated nocturnal

variability may not be. Although given the paucity of nocturnal studies, further work in this field is necessary. Overall, lower values of SDNN confirms that COPD negatively impacts the ANS, reducing heart rate variability and increasing cardiovascular burden. (231)

HR is known to have a strong inverse non-linear relationship with SDNN and this should be corrected for (cSDNN). To our knowledge, no prior study has looked at this in the COPD population. No prior studies have looked at the Poincare indices (SD1 and SD2) in the COPD population either. Two studies have looked at daytime sample entropy values (based on 10minute HR analysis) but had no comparator arm, and did not specify the values of *m* and *r* used in their calculation, making any conclusion difficult. (257) (258) As previously explained, the variability measures derived from AcuPebble RE100 in this study are likely to be somewhat biased by the measuring technique that AcuPebble RE100 uses, and therefore comparison to existing literature is difficult.

However, it is likely that MSE values can be used and suggest that the stable COPD population has decreased multiscale entropy values compared to a non-COPD population, suggesting decreased complexity of the heart rate signal. Decreased complexity of the heart rate and decreased variability is associated with increased systemic inflammation, increased cytokine production, increased cardiovascular mortality and is a negative predictor of outcomes. (259)

4.5.3.2 *Heart rate variability between stable COPD participants and those undergoing an exacerbation*

Many HR recordings from the exacerbating group had significant artefact meaning only 50% of valid admission recordings could be compared with the stable COPD population. As previously described above it is probable that while AcuPebble RE100 measures the mean HR accurately, other calculated HR variability measures are less reliable with evidence of bias, given the multiple layers of filters applied to the recorded sound. Nonetheless, from our small sample size, we found that cSDNN, SD1HR and SD2HR were significantly higher in participants undergoing a COPD exacerbation compared to the stable population, while sample entropy of HR was significantly lower in the exacerbating group (median (IQR) 0.1258 (0.1044 – 0.1568) vs. 0.1607 (0.1355 – 0.1981), p = 0.015). The mean HR showed no significant difference. While we have to be cautious in interpreting these findings, given the bias known to exist with AcuPebble RE100, our results suggest that while participants undergoing an exacerbation have increased HR variability, the complexity of the signal is reduced. These findings are similar to previously published data by Kabbach et al (2017), who used 10-minute daytime recordings comparing COPD exacerbators to stable participants. They also found increased HR variability measures (increased SDNN, SD1 and SD2) in the exacerbating group, but decreased entropy. (260) Another study also found similar results using spectral analyses, assessing the HR variability using frequency domains, showing increased variability in the exacerbating population. (261)

Prior work has shown that patients with stable COPD have autonomic nervous system (ANS) dysfunction, leading to reduced HR variability. (262) However, during an exacerbation patients have increased ANS activity, resulting in increased HR variability, in keeping with the findings from this study. (261) This study has also demonstrated that SD1HR was significantly increased in the exacerbating population compared to stable patients, suggestive of increased short-term variability. This is likely to be a combination of increased respiratory sinus arrhythmia and possibly increased parasympathetic nervous system (PNS) activation. In humans, airway tone is thought to be mainly vagally controlled, (263) and during an exacerbation, there is increased bronchoconstriction, airway narrowing and increased vagal activity in the airway. This may translate into increased PNS activity on the HR and thus increased variability. (260) Respiratory sinus arrhythmia is where the heart rate variability is altered by respiration, (shortened during inspiration and prolonged during expiration). A stressed respiratory system may lead to increased short-term variability of the HR in response to the RR, leading to improved gas exchange. (264) We also established an increase in cSDNN, a global measure of ANS activity and SD2HR, a measure of longer-term variability that incorporates PNS and the sympathetic nervous system (SNS). Patients with COPD exacerbation are also likely to have increased SNS activity, in an increasingly stressed system. This will lead to increased HR variability compared to the stable state. The exact underlying mechanisms of this ANS imbalance are not yet completely understood. It is also important to note, that while in states of stability, a higher heart rate variability is linked to a good overall prognosis, this is unlikely to be the case in this situation, whereby

increased variability, relates to a stretched and heightened ANS with worse clinical outcomes. (260) Finally, it is important to consider the impact of the nebulised medication that forms part of standard treatment in patients undergoing an exacerbation of COPD. Prior studies in stable asthmatic patients have shown conflicting results, with some showing increased sympathetic drive, (265) while others showing no change in heart rate variability. (266) However, to my knowledge, no study has actively investigated the impact of nebulisers on heart rate variability during an acute exacerbation of COPD.

Finally, while this discussion has mainly focused on ANS activity, HR variability is affected by a wide range of different parameters including thermoregulation, chemoreceptors and the circadian rhythm which may also play a role. Moreover, environmental factors, such as stress of being admitted to hospital, bed situation and capacity, and additional medications such as nebulisers, are likely to also play a role.

Sample entropy of HR appears to be significantly lower in patients undergoing an exacerbation compared to stable patients. These results remain true during multi-scale analysis (MSE) of the heart rate recordings, where there was a significant reduction in HR MSE in the exacerbating group irrespective of scale. As previously discussed MSE is more robust to missing data and therefore is likely to be accurate, even allowing for the limitations of AcuPebble RE100 that have previously been discussed. Therefore, it is likely that patients undergoing a COPD exacerbation have decreased complexity in their HR signal. It is worth remembering that complexity is not the same as variability. For example, a sine wave while variable is not complex. Our data is similar to

Kabbach et al (mean (SD) exacerbating SEHR 1.4 ± 0.32 vs. mean (SD) stable SEHR 1.7 ± 0.3, p = 0.007). (260) While our sample entropy values were much lower, a couple of key differences need to be noted. Firstly, their data was conducted over a shorter time duration (10 minutes) and in the day, compared to our nocturnal data over six hours. Secondly, they did not specify the values of *m* and *r* used in their calculation and therefore direct comparisons cannot be made. Nonetheless, their data represents a similar trend to the data in this study. No prior data has conducted MSE analysis in either a stable or an exacerbating COPD patient population, making this data novel.

Lower values of sample entropy suggest a greater degree of regularity and less complexity. Previous work has shown decreased sample entropy in patients with sepsis, (267) cirrhosis (268) and that HR MSE is an independent predictor of death in patients hospitalised for trauma. (269) A reduction in entropy potentially describes reduced system coupling, increased system isolation, which in turn implies a system that is less adaptable to change to added stressors, leading to poorer prognosis. (270) Overall these studies suggest that lower sample entropy and increased system disengagement, are markers of poor prognosis. Moreover, participants undergoing a COPD exacerbation would have a stressed respiratory system and therefore usually strong coupling with the cardiovascular system, (271) meaning the sample entropy in an engaged system should increase to account for this stress. However, we did not see this in our population.

Of note, no associations between any HR measure were found with any of the inpatient admission severity parameters. This is possibly to be due to the small sample size. However, could be due to confounding factors or a genuine lack

of an association or simply that HR measures are poor biomarkers for this purpose.

While no differences were found between HR measures at admission and discharge, there was a trend towards a reduction in HR variability (cSDNN, SD1HR and SD2HR) at day five post discharge, while SEHR increased. While the numbers were too small to conduct meaningful statistical tests, this may suggest that recovery from an exacerbation, 'corrects' HR variability measures back toward baseline stable COPD levels. This was also seen in HR MSE which increased compared to admission/discharge levels. These trends were also seen in the three patients where prolonged follow up data was available.

In summary, it is highly probable that heart rate variability and complexity measures differ between stable and exacerbating patients. Longer future studies are needed to identify the exact point of change. It remains to be seen whether this point occurs prior to perceived symptom onset and whether it can alter management. This may enable us to identify an objective measure of exacerbation commencement, prior to symptoms, allowing earlier treatment and reduced sequelae.

Moreover, this work has highlighted the need for future wearable devices to take into consideration the importance of variability measures, rather than simply focussing on the mean value as this has important clinical implications. Therefore, the design and recording nature of future wearables needs further thought.

4.5.4 Respiratory rate variability analysis

The respiratory rate is affected by a myriad of different signalling pathways including chemoreceptors, mechanoreceptors, locomotion receptors from muscle and joints, the cerebral cortex and the paralimbic system. The breathing pattern can also, to an extent, be voluntarily controlled and is also affected by other factors such as the afferent input from the vagus nerve. It is an integrative process in which the characteristics of current breaths (both tidal volume and respiratory rate) are correlated with previous breaths both in the short term and longer term. This variation is thought to be composed of both random and non-random parts. Short term correlations may reflect automatic or metabolic influences on the respiratory control centre in the medulla. The regulation of breathing variability is important, as a rigid system that has lost variability, means the system cannot adequately respond to stimuli, but a heightened system may lead to overreactions and loss of control. (272-275) To my knowledge, only one prior study (1983) has looked at breathing variability (using coefficient of variation) in patients with COPD and found that it was decreased compared to healthy controls. This study was performed during the day using respiratory inductance plethysmography for 45 minutes in 12 patients with stable COPD and 8 age-and sex matched controls. Coefficients of variation were significantly less for inspiratory time and volume in COPD compared to the healthy controls. (276)

Given the voluntary impact on respiratory rate, it is probable that respiratory rate variability differs from awake and asleep states. In health, respiratory rate variability decreases during non-rapid eye movement (non-REM) sleep, being lowest in N3 (deep sleep). (277) Furthermore, breath-to-breath components

display short-term correlations (longer breath followed by longer breath and vice versa) in both REM and non-REM sleep; but only display long-term correlations during the transition from non-REM to REM sleep, likely due to the cortical influence in REM sleep. (274) The variability of respiratory rate is increased in REM sleep, compared to non-REM sleep but is not as prominent as wakefulness. (277) The decreased variability seen in non-REM sleep is the result of a prominence of short-term autoregression as well as period oscillations. The autoregression is thought to be caused by the central respiratory pattern generator, whereas period oscillations are likely to be due to the chemical / metabolic feedback systems. (275)

Overall, respiratory variability is complex, not yet fully understood and impacted by wakefulness and sleep. While there is some emerging data on respiratory rate variability measures, no prior studies have investigated the Poincare indices (SD1, SD2) and sample entropy of nocturnal respiratory rate in health or disease. Therefore, comparison of my data with pre-existing literature is not fully possible for these measures.

4.5.4.1 Respiratory rate variability between stable COPD participants and the non-COPD group.

The mean respiratory rate for our COPD participants was 17.32 ± 3.20 breaths/minute. This may indicate participants have an increased cardiovascular risk as suggested by Baumert et al (2019). They looked at overnight RR in 2686 men and 406 women and found that post adjustment for age, BMI, smoking, asthma, COPD, OSA, patients with a RR ≥ 16 breaths/min had a significantly higher risk of cardiovascular disease (HR = 1.57, p=0.005). (278) As the data was not normally distributed, non-parametric tests were

conducted to compare to the non-COPD group. COPD participants had a significantly higher meanRR compared to non-COPD group (median meanRR 16.86 (IQR 15.13 – 18.87) vs. 15.64 (IQR 14.26 – 17.00), p = 0.02).

No significant associations were found between any respiratory rate variability measure and COPD disease severity / phenotype. While linear regression suggested a correlation between FEV1 and mean RR and SERR, this correlation was no longer significant following a step wise linear regression analysis correcting for age, gender and BMI. This suggests that different participants with different severities of airflow obstruction have no difference in respiratory rate variability. This not unsurprising, as most participants has moderate-severe disease, with the extremes of disease severity not adequately represented in this cohort. Furthermore, the study is likely to be underpowered given the small sample size to understand the true impact at subgroup levels. The lack of difference in symptom severity and respiratory rate measures is also unsurprising given the subjective nature of these questions and the bias attributed to simply asking patients these questions as part of the study. Moreover, COPD is a heterogenous disease with multiple phenotypes, no one-size fits all, and a poor correlation between symptoms and FEV1. (279) Therefore, it remains unlikely that detailed analysis of just one physiological parameter can differentiate this disease process between different individuals.

Apart from the mean RR, no other differences were found between any of the other respiratory rate variability measures (SDBB, SD1RR, SD2RR and SERR) between stable COPD participants and the non-COPD group. While the measures were numerically higher in the COPD population, none reached

statistical significance. Unlike the HR measures, this is unlikely to be due to measuring artefact or inaccuracy, as the device was positioned over the trachea and the sounds would have had less noise interference compared to picking up the more distant S1 and S2. Furthermore, the data capture was much more accurate for the RR time series.

There could be a few reasons for the lack of differences found. Firstly, the sample size in both cohorts was relatively small. Secondly, it is possible that the data capture for the respiratory rate was of too high a resolution. Similar to the HR measures above, the mean RR was roughly 16 breaths per minute. This suggests that the average inter-breath interval is nearly 4 seconds. Therefore, if AcuPebble RE100 captures data every 2 seconds, there will be a number of repeated RR measurements, which do not reflect the true RR variation. This is similar to the concept described in Figure 6-15 for HR. This is likely the reason MSE analysis of the RR led to significant results, as this employs a coarse grain / zooming out phenomenon.

Multi-scale entropy (MSE) analysis of RR increased in both stable COPD patients and non-COPD group with increasing scale, confirming that the RR time-series recorded was a complex physiological signal, with structural richness. Moreover, MSE analysis showed a significant (F_{group} (1,19) = 39.89, $p<0.001$, $F_{scale}(9,19) = 92.13$, $p<0.001$) increase in the sample entropy values in the stable COPD population compared to the non-COPD group. This difference seemed to be greater at higher scales showing that the increased signal complexity seems to be more apparent when longer-term time scales are considered. This is useful for clinical practice, as it suggests that wearables

with lower resolution data capture (e.g., one sample every 10 or 20 seconds) provides valuable information.

To the best of my knowledge this is novel data and not described in the literature. Through the MSE analysis, the data suggests that participants with stable COPD have a significantly increased sample entropy compared to healthy controls at night. This suggests a respiratory rate that has increased variability and complexity. To understand possible reasons for this, it is necessary to explore changes in sleep patterns in patients with COPD compared to health. Several changes have been noted to occur in patients with COPD during sleep:

1. Patients can often have prolonged oxygen desaturation during REM sleep which have a long duration (of several minutes) and subsequent resolution. (280) The prolonged oxygen desaturation will result in a more engaged or 'panicked' respiratory system compared to health. This will lead to increased signal coupling, as the respiratory system tries to correct the hypoxia. This in turn leads to a more complex system and this increased entropy. (270)
2. People with COPD have a disturbed sleep architecture with frequent arousals and reduced time spent in stage N3 (deep sleep). (281) As described above, this will lead to increased respiratory rate variability and decreased periodicity, with a reduction in short-term correlations that are present in non-REM sleep. This in turn will increase the complexity and sample entropy of the respiratory rate. (275)
3. In COPD, during non-REM sleep the basal metabolic rate (responsible for the periodicity / regularity) and the central ventilatory drive

(responsible for short-term autoregression) are decreased. (282) This in turn will lead to increased variability and entropy.

4. During sleep there is inspiratory muscle hypotonia leading to a reliance on the diaphragm to maintain ventilation. However, in COPD the diaphragm is inefficient due to hyperinflation, and this is accompanied by falls in minute ventilation. (281) This overall, leads to a system that must be more engaged, with likely increased respiratory rate coupling to maintain adequate ventilation. A more engaged system will lead to increased variability / complexity and higher entropy.

In summary, it is possible that patients with stable COPD have increased nocturnal respiratory rate variability and complexity that can be explained by a more 'switched on' or engaged or heightened respiratory system. This may in turn lead to a loss of control or over-reactions of an already stretched system, leading to an aberrant loop gain pathway. Only one prior study has looked at daytime respiratory rate variability in COPD patients and found it to be reduced, but this study only included eight patients and used the coefficient of variation analysis only. (276) A previous study using daytime respiratory rate measurements also found that the respiratory rate variability was reduced in patients with chronic asthma. (283) Clearly further work in this field is necessary to better understand the differences in respiratory rate variability both during the day and at night.

4.5.4.2 Respiratory rate variability between stable COPD participants and those undergoing an exacerbation

No previous study has investigated respiratory rate variability in a patient undergoing a COPD exacerbation, making these findings novel.

The mean RR between groups showed no significant differences. Respiratory rate variability measures (SDBB, SD1RR and SD2RR) were significantly higher in patients undergoing an exacerbation compared to the stable population. Sample entropy of RR was numerically higher in patients undergoing an exacerbation but did not reach statistical significance. However, MSE analysis of RR showed that sample entropy was significantly higher [F_{group} (1,20) = 40.703, p<0.001, F_{scale}(9,20) = 51.434, p<0.001] in the exacerbating group compared to the stable group, irrespective of scale. This difference was more apparent at higher scales, suggesting that the increased signal complexity becomes more apparent when longer-term time-scales are considered. This is very useful for clinical practice, as it suggests that wearables with lower resolution (e.g., one sample every 10 or 20 seconds) provide more valuable information than higher resolution data.

This data suggests that patients undergoing a COPD exacerbation have increased variability and complexity in their RR signal compared to the stable population. There are several possible reasons for this. First, while both recordings were nocturnal, there was no sleep diary, and therefore the hospitalised patients may not have been asleep during the analysis time. This would bias the results, as an awake state has increased RR variability. Second, hospitalised patients are known to have poorer sleep quality with frequent night-time intrusions, (284) meaning that they may spend less time in

non-REM deep sleep, meaning that RR variability increases. This would imply that the changes seen, are due to poor sleep, rather than representing true underlying physiological changes in the actual RR. However, a recent cohort study on hospitalised COPD patients, found that while COPD patients averaged 34 fewer minutes of nightly sleep, their sleep quality (assessed using the Karolinska Sleep Diary) was no different. (285) Therefore, while it is probable that hospitalised patients sleep architecture differs, it is unlikely to account fully for the increased variability seen. Third, patients undergoing an exacerbation were hypoxic, leading to a metabolic imbalance, and this is likely to increase respiratory rate coupling and engagement, leading to increased variability and complexity. Fourth, during a COPD exacerbation, there is greater skeletal muscle dysfunction (286) and increased hyperinflation, (287) meaning reduced efficacy of both the inspiratory muscles and the diaphragm. This in turns means a fall in minute ventilation and leads to increased engagement of the respiratory system with increased complexity. Finally, COPD patients undergoing an exacerbation will be breathing in a state of dynamic hyperinflation, resulting in increased activity of the stretch-sensitive afferent fibres, and will have increased systemic inflammation leading to activation of the bronchopulmonary C fibres. Both are vagal afferent nerves, and dysregulation of these nerves can lead to increased smooth muscle tone, mucous secretion and cough. (288) Ultimately this will lead to a respiratory system that is heightened and more complex given the large number of interactions occurring at multiple scales. This will lead to increased variability and complexity of the respiratory system, which is under active stress.

No significant associations between any RR measure were found with any of the inpatient admission severity parameters. This is likely to be due to the small sample size, aforementioned hospital environment and/or medications.

Only a small number of patients could be compared with regards to admission vs. discharge vs. post discharge. Therefore, these results need to be interpreted with caution given the small sample size.

While no differences were found between RR measures at admission and discharge, there was a trend towards decreasing variability and complexity at five days post discharge. No apparent change in mean RR could be seen. MSE analysis of RR showed that at lower scales, there was no apparent difference in sample entropy comparing admission, discharge, and five days post. This difference was more apparent at higher scales, once again suggesting future wearables should be of lower resolution to capture these differences. This may suggest that during the recovery phase of a COPD exacerbation, variability decreases. Therefore, it is probable that in the lead up to an exacerbation, variability is likely to rise and finding this point is vital in developing algorithms to objectively detect an exacerbation. Interestingly, in the 3 patients followed for a longer duration, there seemed to be minimal differences in SDBB and SD2RR, while SERR significantly decreased ($R2 = 0.297$, $p<0.001$).

In summary, during an exacerbation, the stress placed on the respiratory system leads to a more engaged and coupled system that is actively dealing with an acute state. This leads to increased respiratory rate variability and complexity.

4.5.5 Airflow variability analysis

There is limited prior data using DFA analysis on airflow data. In brief, DFA quantifies long-range power law correlations of a non-stationary time series, providing a quantitative parameter (alpha). A power law correlation is a functional relationship between two quantities, whereby a relative change in one, quantity leads to a relative change in another. Long-range correlations simply indicate that for example a large inter-beat HR interval or a higher airflow rate is more likely to be followed by a large interval or flow rate and vice versa. It is important to note that in physiological time-series the scaling exponent (alpha) is not always constant (i.e., independent of the actual scale) and therefore cross-overs exist. This can mean the scaling component differs for different ranges of scales. (234, 289) (290) The values of the scaling exponent (alpha) has various meanings: (234)

- $\alpha = 0.5$ is suggestive of white noise and completely random fluctuation, and thereby a signal that has no correlations.
- $0.5 > \alpha < 1.0$ indicates positive autocorrelations and persistent long-range power-law correlations.
- $0 < \alpha < 0.5$ indicates anti-correlation whereby large and small values of the time series are likely to alternate.
- $\alpha = 1$ corresponds to 1/f noise or pink noise. This is whereby the signal has a frequency spectrum whereby the power / count / intensity is inversely proportional to the frequency of the signal. Any physical signal can be decomposed into many discrete frequencies (a spectrum). With pink noise, lower frequencies have a higher count compared to higher frequencies. (291)

- α ≥ 1 correlations exist but are not of a power-law form.
- α = 1.5 indicates Brown noise. The spectral density is inversely proportion to f^2, meaning that there is a higher count (more than pink noise) at lower frequencies. The change in the signal from one moment to the next is still random, but unlike white noise, there is greater energy / intensity at lower frequencies.

Finally, the alpha value can also be viewed as an indicator that describes the 'roughness' of a time-series, with higher values representing a smoother time series. (234)

DFA analysis showed that the pattern of airflow variability is fractal-like. This is similar to previous work by Saatci et al (2020) but they used a slightly different measure (multifractal DFA). (292) For the first time I have demonstrated that nocturnal airflow variability in non-COPD patients, stable COPD patients and those undergoing an exacerbation, have two cross-over points with three exponents (α1, α2 and α3). This differs from a HR and oxygen saturation time series, where prior work has shown only one cross over point. (234) (247)

4.5.5.1 Airflow variability between stable COPD participants and the non-COPD group.

This data has shown that on very short scales (corresponding to roughly 3 seconds) the fluctuation of airflow is stable and smooth with a high α1 value. While participants with COPD had statistically significantly lower α1 compared to the non-COPD cohort (median 1.66 (1.63 – 1.67) vs. 1.68 (1.66 – 1.68), $p < 0.001$), it is unlikely that this is clinically relevant.

At an intermediate scale (corresponding to roughly 30 seconds), participants with COPD had a significantly higher α2 value compared to the non-COPD cohort (median 0.29 (0.26 – 0.31) vs. 0.24 (0.21 – 0.27), p< 0.001). However, both values were less than 0.5, suggestive of anti-correlation at these scales. This means that a higher rate of airflow is followed by a lower rate of airflow. This seemed to be more prominent in the non-COPD cohort (i.e., a lower alpha2 value). This may be explained by the concept of memory in time-series. This is where past information of the time-series influences its present state. It has previously been shown that healthy subjects have less memory than in certain disease states, such as heart failure. (293) In this example, each heartbeat keeps a longer memory of previous heart beats. This can be a disadvantage to respond to a changing environment, delaying necessary change. Participants with uncontrolled asthma have also been shown to have a longer memory than healthy controls. (293) Therefore, in our sample, COPD patients may have a longer memory, meaning less anti-correlation, as they are 'holding' on to the increased / decreased airflow for longer and thus changing slower.

Finally, at larger scales (over 30 seconds), there was no significant difference between COPD participants and the non-COPD cohort (median 0.69 (0.65 – 0.66) vs. 0.72 (0.66 – 0.78). The alpha 3 values were above 0.5 but less than 1, meaning at larger scales airflow variability demonstrated long-range power law dynamics and was positively autocorrelated.

In summary the DFA analysis suggests that stable COPD patients have a longer memory compared to the non-COPD cohort. This means that they are not able to vary their breathing pattern as quickly as non-COPD patients,

meaning that they are 'holding' on to the past and thus have less adaptability and flexibility to additional stressors.

4.5.5.2 *Airflow variability between stable COPD participants and those undergoing an exacerbation*

For short-term scales (corresponding to roughly 3 seconds) the fluctuation of airflow in both groups was smooth with a high α1 value above Brown noise. While the exacerbating group had a significantly lower α1 value, it is unlikely that this is clinically relevant.

At an intermediate scale (corresponding to roughly 30 seconds), there was no difference in the α2 value between both groups. Both values were less than 0.5, suggestive of anti-correlation, whereby a higher rate of airflow is followed by a lower rate at this scale. Both values were higher than the non-COPD group, suggesting once again, that patients undergoing a COPD exacerbation are likely to have increased system memory. This means that they are slower to 'alternate' their airflow rates that a healthy individual as they are 'holding on' to the previous airflow rate. This means they are less adaptable. This has previously been seen in asthmatics when studying respiratory rate. (293)

At longer scales (above 30 seconds), exacerbators had a significantly lower α3 value compared to the stable population (median (IQR) 0.5000 (0.4676 – 05578) vs. 0.6931 (0.6509 – 0.7931), $p<0.001$). This suggests that while stable COPD patients demonstrate long-range power law dynamics and positive autocorrelation at longer scales (whereby higher airflow rate is followed by higher and vice versa), the exacerbating population have an α3 of 0.5, which is suggestive of white noise and completely random fluctuation. This means at

longer scales there is no correlation in the airflow and the airflow pattern is completely random. COPD exacerbations have increased upper and lower airway inflammation as well as bronchoconstriction, oedema and increased mucous production. This can lead to expiratory flow limitation, narrow calibre airway and increased turbulence of flow. (287) This may explain why the airflow becomes more akin to white noise and becomes completely random. This is also compounded by nebulised therapy. Interestingly while most changes in COPD occur in the small airways, AcuPebble RE100 recording of the large airway still demonstrates random airflow.

A prior study using DFA on daily isolated peak flow measurements, showed that higher alpha values were associated with increased exacerbation frequency. (233) However, a key and important difference in this study was using daily isolated peak flow measurements, rather than continuous measurements of airflow at very high resolution. Furthermore, this data had no cross over points in their data. Therefore, true comparison with this work is not possible.

No differences were found in any alpha values at admission or discharge. However, five days post discharge, importantly alpha 2 decreased and alpha 3 numerically increased. This suggests that during the recovery phase of an exacerbation, at intermediate scales, there is more anti-correlation (i.e., lower alpha 2 value), meaning less memory, and thus more adaptability. The increase in alpha 3 means, at longer term scales, airflow is becoming less random and more positively autocorrelated. Interestingly, these trends were not seen on longer term follow up of the three patients. This may be due to a small sample size, however, could also potentially imply that the airway

inflammation and obstruction may take longer to recover than symptom recovery. Currently the end of an exacerbation is defined as a return to pre-exacerbation state, which will be largely subjective based on patients' symptoms. (294) However, perhaps the airway inflammation lasts longer that symptom improvement, meaning alpha 3 will not increase for a considerable while longer. While this is all theoretical, it merits further investigation with longer term studies.

4.5.5 Limitations

There are several limitations to this work. Firstly, study participants used the AcuPebble RE100 device for a varying number of nights with a large range, with only one participant completing the 30-day period. This is likely to introduce bias in the results when comparing mean values from each participant. However, given all patients had stable disease, it is unlikely that would make a significant difference to the mean values. Second, there was a great deal of artefact from the HR and airflow recordings, due to the way measurements were recorded by the device leading to a high type 2 (beta) error. In terms of HR, this had little bearing on the mean values but impacted variability measurements. Therefore, future wearables need refinement in their filtering algorithms to achieve more accurate variability measurements. Third, we took the first 6-hours of recording, without knowing when participants fell asleep and must acknowledge that sleep times may differ, and so we may be comparing slightly different sleep stages. Although by using a 6-hour time window we will have accounted for both REM and non-REM sleep time. Fourth, participants did not have contemporaneous spirometry, largely due to the COVID-19 pandemic. Fifth, our non-COPD group was historical and not

age matched, meaning that comparisons that have been, need to be interpreted with a degree of caution. Furthermore, the non-COPD group sample, only had a one-night recording which could impact the results further. Sixth, while we used the median nocturnal time to use as the start point of our analysis for the exacerbating population, no sleep diaries were given to patients. Therefore, we may have captured some data while COPD exacerbators were awake. This could lead to some bias, as there is evidence to suggest HR and RR variability differs during sleep compared to wakefulness. Seventh the patients admitted to hospital may have started their actual exacerbation at different times, i.e., one participant may have presented on day 1-2 of their exacerbation, but another may have trialled management at home and been on day 5-6 of the exacerbation. In future studies, a retrospective symptom diary would be useful to pinpoint the exact start of their symptom onset. Lastly the overall sample size was small, and the study is likely to be underpowered. Eighth, our sample size was small to detect differences post discharge variability changes. Finally, the COPD diaries were not accurately completed by anyone, meaning a lack of available data to analyse. This could have been useful as subtle differences in symptoms may have been reflected in the various time-series.

However, even with this small sample size, differences were observed in several parameters, and we have also shown that a study of this nature was feasible and possible.

6.6.7 Conclusion

In conclusion, I have used a novel wearable device to obtain signals from participants with both stable and exacerbating COPD over multiple successive

nights to gain insight into their HR, RR and airflow variability. The device proved easy to use and in the main acceptable to participants. The data demonstrated that a longer time duration of analysis yields more consistent results and ensures incorporation of both REM and non-REM sleep cycles. While the device was accurate for the mean HR and mean RR measurement, variability analysis is likely to be less reliable. For HR this is likely due to multiple filtering techniques that remove subtle variations in the data. For RR this is likely to be because the data resolution was too high and needs to be looked at in a 'zoomed out' fashion.

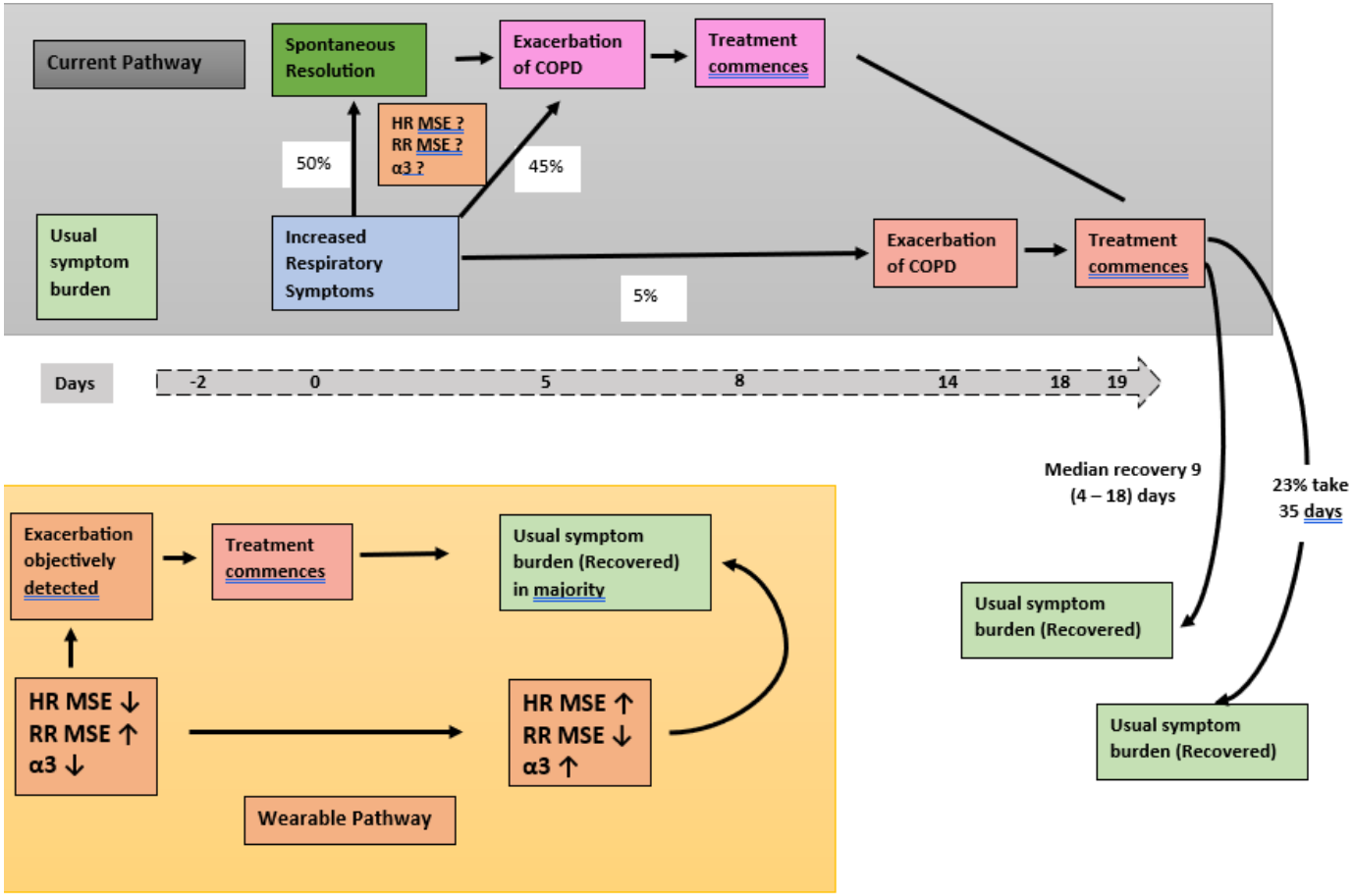
Exacerbating patients had increased HR variability but decreased complexity; increased RR variability and complexity and on longer scales had random airflow with no correlations compared to the stable population. It is clear from this work, that differences exist between stable and exacerbating COPD patients, but these differences are only apparent when linear and non-linear analysis methodology is used.

Future work needs to focus on identifying the point(s) at which variability measures change in a patients' exacerbation journey, above day-today variations, and whether this can be picked up objectively prior to symptoms, such that treatment can be started earlier and thus avoid severe sequalae. Figure 4-30 summarises my work in stable and exacerbating patients and highlights areas of future work.

We have assessed AcuPebble RE100 in participants with both stable and exacerbating COPD. It's utility in other respiratory conditions such as OSA merits review. AcuPebble SA100 is a similar device, already validated for OSA

diagnosis and in the next chapter I reviewed whether it could be used as a monitoring tool in a group of OSA patients undergoing continuous positive airway pressure therapy.

Figure 4-30 The potential future of wearables and physiological variability analysis in detecting a COPD exacerbation. Adapted from (38) (40)



CHAPTER 5

5. Chapter 5 – The use of a novel wearable medical device for remote monitoring of patients with obstructive sleep apnoea on continuous positive airway pressure therapy.

5.1 Background

Continuous positive airway pressure (CPAP) therapy is the globally accepted gold-standard treatment for obstructive sleep apnoea (OSA), virtually eliminating OSA (by normalising the AHI), improving quality of life, decreasing daytime sleepiness and probably reducing medical sequelae. (295) However, in some patients a high residual AHI (and therefore OSA) may still be present despite adequate treatment with CPAP. This patient population will suffer on-going daytime somnolence, sleep apnoea symptoms and potentially ongoing cardiovascular risk. This will lead to a reduction in their concordance, due to perceived lack of benefit, which will increase their residual AHI further, creating a vicious cycle. Therefore, reliable monitoring of their CPAP and underlying AHI is necessary to optimise treatment.

Ideally CPAP should be used for the entire duration of sleep, but this is not the case for a significant number of patients. Furthermore, while CPAP machines can detect the residual AHI, the effective AHI remains unknown. The effective AHI, a term introduced by Boyd et al and can be defined as the AHI measured over the entire duration of sleep and includes both time on and off CPAP therapy. In a small sample of patients (n=28), they found that in participants

who used CPAP for < 6hours/night, 63.5% of participants had an effective AHI in the moderate-severe category. (75)

Currently CPAP monitoring in most centres in the UK is conducted via remote telemonitoring, whereby the CPAP machine inherently calculates nocturnal usage and the residual AHI (i.e., the patients' AHI while using the machine). This is either available via a direct upload to a GDPR compliant cloud, or through a SD card which can be manually downloaded. While CPAP machines can store airflow and pressure data, the algorithms between different manufacturers vary. A review by the American Thoracic Society concluded that while the actual usage can be reliably determined from the machine algorithms, the actual residual AHI and data around mask leak is not easy to interpret. (74) Furthermore, some studies have found that this is especially the case in relation to detecting residual hypopnoeas. (296-298) Therefore a more accurate and simple system is needed to determine both usage and residual events, that is standardised, reliable, and independent of machine manufacturer.

Overnight oximetry recordings have previous been used to monitor patients on CPAP therapy. However, there are some limitations to this strategy. Firstly, studies comparing the diagnostic utility of oximetry for OSA have found decreased sensitivity and specificity in patients with mild-moderate OSA compared to severe OSA. (135, 299, 300) This suggests that in treated patients, who are likely to have decreased disease severity, the accuracy is likely to be limited. Second, there is a paucity of data on how well overnight oximetry works while patients are on CPAP compared to gold standard. Third,

oximetry's only capture desaturation events and therefore miss events that occur without desaturation (i.e., some apnoeic events and arousals).

Recently Epstein et al (301) investigated whether a home sleep apnoea testing kit (WatchPAT®200, Itamar Medical, Israel) could accurately determine the AHI while patients used CPAP therapy. They concluded that the WatchPAT®200 AHI was significantly higher than simultaneously automated CPAP detected AHI in nearly half of patients with clinically suspected residual sleep disordered breathing. However, a major limitation of this study was the presumption that WatchPat® could accurately diagnose the AHI in patients on CPAP, without a gold standard comparator arm. Moreover, WatchPAT® can be uncomfortable for patients given its use of peripheral arterial tonometry, meaning the sensor has to be quite tight on patients' fingers.

It is also useful to note, that recently Foresi et al, have shown that built-in-software analysis on one brand of CPAP machine showed good accuracy with a gold standard multi-channel sleep study in detecting the residual AHI (bias of 0.57events/hr (95%CI -3.30 – 4.45). However, this study used a specific brand of CPAP device. (302) Moreover, the study, titrated CPAP pressures first to adequately reduce the AHI and only waited a further 2 days prior to conducting a sleep study. This would have led to an inherent bias, as these patients were optimised just prior to the recording and all patients included in the study had excellent control (mean AHI 2.6 ± 2.4 events/hr).

Therefore, further research into accurate ways of monitoring both the residual and effective AHI while using CPAP is important to try and risk stratify patients and also potentially suggest an individualised target for hours of nocturnal

CPAP based on initial disease severity. This would especially help in patients who are struggling with CPAP concordance. For example, four hours of CPAP use may be adequate for someone with moderate OSA but not enough for someone with severe OSA. This idea has been illustrated previously in Figure 1-6.

AcuPebble SA100 is a medical device, similar to Acupebble RE100, which was created for the purpose of improving the diagnosis of OSA and has a high positive (96%) and negative (99%) predictive value when compared with a cardiorespiratory-polygraphy. Furthermore, the study demonstrated that this device can be used by patients, without requiring professional assistance at home. (145) Therefore, we aim to investigate whether AcuPebble SA100 can also be used as a monitoring tool to detect both the residual and effective AHI in patients undergoing CPAP therapy.

5.2 Aims

The primary aim of this study was to determine whether AcuPebble SA100 can accurately determine the residual AHI in patients with OSA on CPAP therapy, using a simultaneous cardio-respiratory polygraphy as the gold standard comparator.

The secondary aims of the study were:

- To determine whether AcuPebble SA100 is more accurate than the CPAP machine in detecting the residual AHI in patients with OSA on CPAP therapy.

- To determine whether AcuPebble SA100 can accurately determine the effective AHI (this includes time spent on and off CPAP, i.e., the whole night).
- To determine whether AcuPebble SA100 is acceptable and comfortable for patients to wear while using CPAP therapy.

5.3 Methods

5.3.1 Ethical approval

This study received ethical approval from the Health Research Authority (IRAS ID: 311874, REC reference 22/SC/0272); and was sponsored by Royal Free Hospital NHS Foundation Trust, where it was conducted.

Under the scope of this study, AcuPebble SA100 was the novel sensor that was used. It is a CE marked device, and for this study was used within the scope of its intended purpose as a medical device as a monitor for participants on treatment.

5.3.2 Inclusion and exclusion criteria

Inclusion criteria:

- Patients with an initial diagnosis of moderate/severe OSA (defined as an AHI ≥ 15events/hr made on a full polysomnography, limited cardiorespiratory polygraphy or other validated home sleep study) with no evidence of nocturnal hypoxia (defined as spending <30% of the night with saturations <90%).
- Patients who have been established on CPAP therapy > 3 months
- Patients who are deemed compliant on CPAP therapy (average use ≥ 4hours/night for ≥ 70% of the last 28 nights).

Exclusion criteria:

- Age <18
- Subjects not fluent in English, or who have special communication needs
- Known allergy to adhesive dressing

- Subjects with physical or mental impairments who would not be able to use the device and technology on their own
- Subjects with implantable devices
- Subjects with stridor
- Subjects unable to or unwilling to give consent
- Subjects on non-invasive ventilation (NIV) or bi-level positive airway pressure (BIPAP)

5.3.3 Study protocol

This was a prospective observational study conducted at the Royal Free London NHS Foundation Trust which at the time of study had a total of 1899 patients with a diagnosis of OSA on CPAP therapy.

Potential participants for this study were recruited from the sleep and ventilation service at Royal Free Hospital. This service is a tertiary sleep and ventilation service in North London. All patients under this service who are on CPAP therapy for moderate / severe OSA and have consented, have their CPAP usage monitored remotely. This information is available on a secure password protected GDPR compliant website accessible only to the direct care team looking after the patient. This is the current standard of practice at the Royal Free Hospital.

Participants were screened through review of medical records (to identify whether they met the inclusion/exclusion criteria), and their CPAP usage information (to ensure they were compliant on CPAP and had been using it for at least 3 months). We then randomly selected patients who met the eligibility criteria from this existing database of patients. Participants were called in

advance of their study visit and if agreeable the participant information sheet was sent to them by post or email, according to patient preference.

Study Visit 1

Participants were consented for a 2-night study while using their CPAP. At the initial study visit they were asked to fill in two questionnaires:

1. Epworth Sleepiness Scale – a commonly used subjective measure of patient's sleepiness (Appendix 7.7.1)
2. A baseline symptom questionnaire ('Sleep Clinic Questionnaire (SCQ)) – created specifically for this study to gain some understanding on whether participants are suffering from common OSA symptoms). See section 7.7.2

We collected baseline information from the participant and the medical records including age, gender, ethnicity, body mass index (BMI), original sleep study (type, date, and outcome), comorbidities, smoking history, CPAP data (including average use over the last 28 days; average number of hours used on the days used; average pressure requirement; average residual AHI over the last 28 days; any leak recorded).

Participants were pseudo-anonymised and given a trial identification number, which was used to set up the monitoring devices they had been asked to wear.

Participants were asked to wear the following devices (below) for the entire duration of their sleep study for two consecutive nights. The average use of CPAP over the preceding 3 months was noted and patients were asked only to use the CPAP for the same duration (rounded to the nearest hour) to reduce bias on the nights of the study. The participants were asked to use both

monitoring devices (below) for the duration of their sleep. They were also asked to note down the time each device was put on and the time CPAP was put on (‘D’on) and off (D’off). The CPAP machine automatically downloads data including the residual AHI, which is visible on a secure password protected website that patients have already consented to. Therefore, the CPAP data could be directly compared to both the following devices.

The two monitoring devices participants were asked to wear for the entire duration of sleep were:

1. **AcuPebble SA100** – Participants were all provided with a research mobile phone with the application installed and given basic information at the study visit on how to use the device. The signals recorded from AcuPebble SA100 are automatically encrypted and transmitted to a secure website that is compliant with General Data Protection Regulations (GDPR). The device can automatically diagnose OSA.

   For this study, we only used the 4% desaturation threshold as this is the current clinical standard at Royal Free Hospital to measure disease control. While this gave the effective / whole night AHI, data was re-analysed to match the time that CPAP was used, thus giving us the residual AHI as well.

   Participants were given a very basic instruction sheet to aid them to use the device. The main purpose of the instruction sheet was to serve as a reminder of how to open the application on the mobile phone. Participants were asked to go through the following steps for each of the nights of the study:

i. Link AcuPebble SA100 to the mobile phone application (by starting a new study on the application itself, with the device in proximity)
ii. Attach the adhesive provided to AcuPebble SA100 (a video on the application showed participants how to do this)
iii. Attach AcuPebble SA100 onto the front of their neck (anywhere between the suprasternal notch and Adam's apple).
iv. Press 'start recording' when ready.
v. Press 'stop recording' the following morning on waking.
vi. Allow the device to download the data and automatically run a diagnostic algorithm yielding the diagnostic results for night one.
vii. Repeat above steps with a new adhesive for the second night.
viii. Device and phone needed to be charged in between nights.

During their study visit, participants were asked to carry out a 'mock trial' on how to use the system and to ask questions if there were any doubts.

The device automatically gives a diagnosis and AHI which was evident on the patients' own downloaded application. The signals were encrypted automatically by existing software and subsequently

transmitted to a password protected, secure website, compliant with GDPR.

2. Domiciliary cardiorespiratory polygraphy (Embletta MPR PG ambulatory (unattended) polygraph sleep monitor (Stowood scientific instruments ltd)) –reference standard. The following signals were used for analysis: thoracic and abdominal piezoelectric respiratory movements sensors; peripheral pulse oximetry; nasal thermistor air-flow sensor; snore and body position. It is a device that meets the AASM technical adequacy requirements to be considered gold standard for ambulatory diagnosis of the disease. Please see Appendix 7.6 for further details on diagnostic criteria and manual scoring criteria. Participants were shown how to put this device on at their study visit and were told to wear and use this device for both nights along with AcuPebble SA100.

   The device was automatically programmed to start and stop recording at set times.

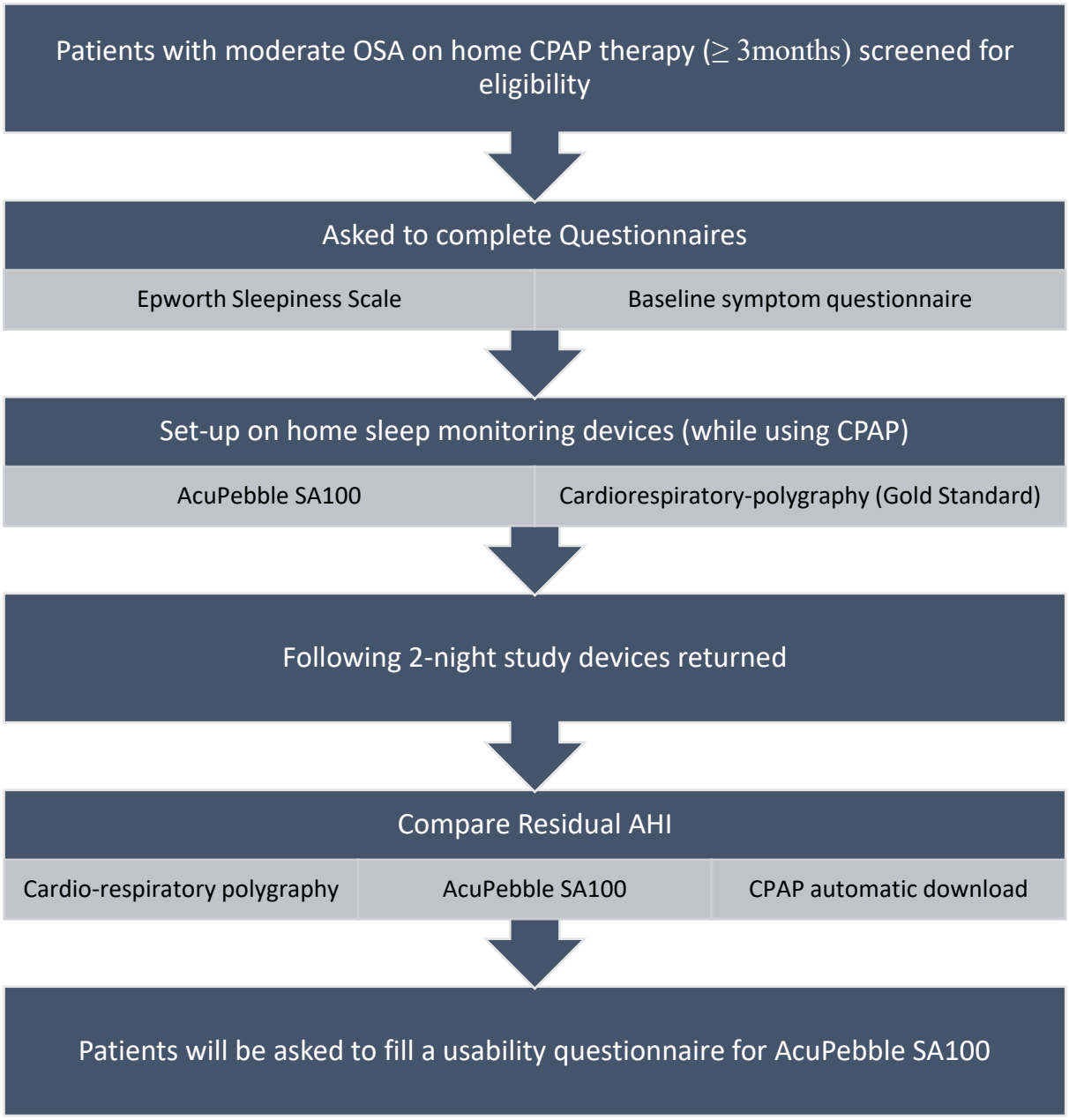
   The sleep studies were scored / analysed by two independent scorers in a blinded fashion. Both scorers were also blinded to the results from AcuPebble SA100 until our analysis was completed. The sleep studies were scored using the AASM criteria with a 4% oxygen desaturation threshold used for scoring hypopnoeas. Initial analysis was conducted using the specific times of CPAP use (giving the residual AHI). If the entire duration of sleep as noted on the sleep study differed by more than 30 minutes compared to the CPAP start / end times, the studies were re-analysed for this duration, giving the effective AHI. We also

calculated the mean saturations, the oxygen desaturation index, and the percentage of time spent with saturations less than 90%. The overall duration of sleep was noted as the index time (overall time minus the movement time).

If the difference in the start / stop times of CPAP vs. AcuPebble SA100 / multi-channel sleep study was ≤ 30minutes, the data was not re-analysed (to get the effective / residual AHI). This value was assumed to be the residual AHI. The reason this time gap was chosen, was that clinically we felt this was unlikely to make a significant difference in the calculated residual / effective AHI. Therefore, in this instance, the participant had effectively used the device for the entire duration of the night and the effective and residual AHI were the same.

Following completion of the study, participants were asked to fill out a usability questionnaire for AcuPebble SA100. Participants were then asked to return both devices either in person or by an arranged courier.

5.3.4 Study flow chart



5.3.5 Statistical analysis

Sample size calculation

The main statistical test used in this instance was a Bland-Altman analysis to check the agreement between measurements obtained by AcuPebble SA100, CPAP and the gold-standard multi-channel polygraphy. The outcome variable was AHI. An assessment of the agreement in the AHI produced by AcuPebble

SA100 vs. gold-standard and AcuPebble SA100 vs. CPAP was conducted. Therefore, the following parameters were used in the power calculation:

Mean of any paired differences: 2

Standard deviation of paired differences: 3

Power 95%

Type 1 error: 5%

Since there were three devices and two comparisons with repeated measures, the type 1 error was adjusted for multiple testing using the Bonferroni method and gave a value of 0.025. This was used to compute the required sample size of 37. In this study repeat measurements were taken over two days and therefore I needed to recruit 18.5 patients to achieve 95% power of detecting a true difference with 0.025 probability.

Statistical Analysis

All the statistical analysis was conducted using the software Statistical Package for the Social Sciences (SPSS). Baseline demographics were tabulated. The internal validity of the manual sleep study scoring from both scorers of the gold standard multi-channel polysomnography was assessed using the intraclass correlation coefficient using a two-way mixed effects method with consistency, as previously described by Khoo et al. (235) The mean values from both scorers was used as the ‘gold standard’ AHI. This was then used to compare to the CPAP or AcuPebble SA100 AHI using Bland Altman Plots.

The Bland-Altman plots were constructed in MATLAB programming software using freely available coding algorithms. Two plots were constructed. One using the mean of paired differences on the x-axis and another using the gold standard measure on the x-axis as first described by Krouwer et al. (303) The same process was used for residual and effective AHI.

Finally, we assessed the acceptability and comfort of AcuPebble based on questionnaires and usability defined as:

- Percentage of patients who used the system correctly.
- Percentage of patients who completed the test, returning valid signals.
- Usability answers in the questionnaire

5.4 Results

For the study 136 participants were screened of which 30 met eligibility criteria and 19 were consented. One participant withdrew their consent prior to starting the study. One participant did not use their CPAP or any of the test equipment for either night. Therefore, CPAP data was available for 17 participants (15 male, 2 females; mean (SD) age 55 (14) years), 14 completed a two-night study and three only used CPAP for one night, resulting in a total of 31 studies. Gold-standard multi-channel sleep data was available for 11 participants, with the remainder having either no data or very poor-quality data that was not usable. Of these 11 participants, eight managed a two-night study, while three only managed one night, resulting in a total of 19 studies which were of sufficient quality. Valid AcuPebble SA100 data was available for 14 participants, with seven manging both nights and seven managing one night. This gave a total of 21 valid recordings. Overall, 11 recordings from nine participants had good quality multi-channel sleep study and AcuPebble SA100 data allowing for comparison. In summary, 19 recordings were available to compare CPAP vs. gold standard and 11 recordings were available to compare AcuPebble SA100 vs. gold standard. This is summarised in Figure 5-2. Table 5-1 shows the participants baseline characteristics and medical comorbidities and Table 5-2 shows their original sleep study data, CPAP data and symptom questionnaire data.

Figure 5-1 Study flow diagram

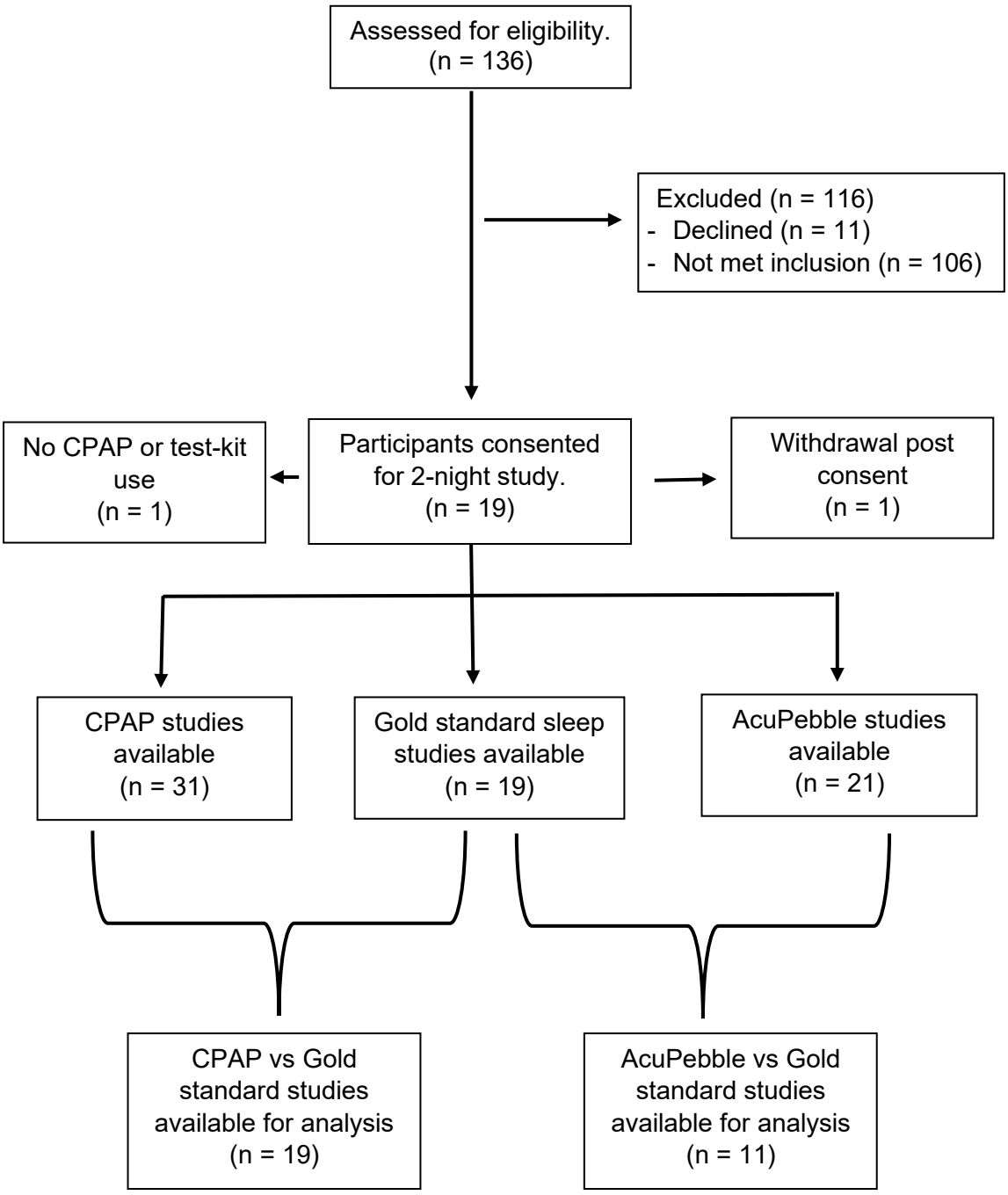


Table 5-1 Baseline characteristics of participants (n = 17)

Baseline characteristic	n (%), mean ± SD, median (IQR)
Male	15 (88)
Female	2 (12)
Age (years)	55 ± 14
Body Mass Index ($kg.m^2$)	34.6 (32.7 – 37.7)
Never smoker	6 (35)
Ever-smoker	11 (65)
Pack year history	25 (12 – 42)
Mobility Independent Stick	 16 (94) 1 (6)
Independent with regards to activities of daily living	17
Medical Co-morbidities	
Asthma	3 (18)
Atrial fibrillation	0
Cerebrovascular disease	2 (12)
Hypercholesterolaemia	5 (29)
Hypertension	6 (35)
Ischaemic heart disease	1 (6)
Type 2 diabetes mellitus	3 (18)

The participant who did not use CPAP or any of the devices was excluded from the background demographic data.

Table 5-2 Sleep study and CPAP use characteristics for participants (n = 17)

Characteristic	n (%), mean ± SD, median (IQR)
Original sleep study data	
Type of sleep study: • Multi-channel sleep study • WatchPat® study	 • 4 • 13
AHI (events/hour)	54.5 (33 – 75.8)
ODI (events/hour)	47 (30.1 – 76.4)
Mean Saturations (%)	93 (92 – 94)
Time spent with saturations below 90% (%)	9.9 (2.5 – 18.9)
CPAP usage prior to study	
Type of CPAP device: Philips Lowenstein	 11 (65) 6 (35)
Average nightly CPAP use in the last 3 months (mins)	414 ± 62
Baseline symptom questionnaire	
Epworth Sleepiness Score	4 (3 – 11)
Baseline symptom severity score*	4 (2 – 6)
Average hours of sleep	7 ± 0.7
Average time taken to fall asleep (min)	21 ± 15
Presence of nocturia	9 (53)
Driving statistics post starting CPAP (n = 10)	
Road traffic accidents	0
Episodes of head bobbing while driving	1 (10)
Hitting the rumble strip while driving	1 (10)
Using alerting manoeuvres while driving	2 (20)

* The baseline symptom severity score was developed for this study to look objectively at the frequency of common symptoms in OSA. Higher scores indicate increased symptom burden. The total score is out of 24.

5.4.1 Interrater reliability of multi-channel sleep study scoring

A total of 19 sleep studies were available from 11 participants, with the remainder having either no data available or very poor-quality data available. Two of these studies had a high percentage of oxygen saturation trace artefact but preserved nasal flow tracings and were included given the small overall numbers available for analysis. The intraclass correlation coefficient values for all the measured and scored parameters from the sleep study are shown in Table 5-3.

Table 5-3 Intraclass correlation coefficients (ICC) for interrater reliability of multi-channel sleep studies (n = 19)

Analysis variable	**Scorer 1 Mean ± SD**	**Score 2 Mean ± SD**	**ICC**
Index / Analysed time (min)	407 ± 70	403 ± 70	0.997
Overall AHI (events/hr)	3.3 ± 3.6	2.5 ± 3.1	0.984
Obstructive apnoea (events/hr)	0.7 ± 0.9	0.2 ± 0.3	0.532
Obstructive hypopnoea (events/hr)	2.4 ± 2.6	2.1 ± 2.4	0.990
ODI (events/hr)	3.4 ± 3.5	3.3 ± 3.6	0.997
Mean sats (%)	93.9 ± 1.4	93.9 ± 1.4	0.999
Time below 90% (%)	2.6 ± 4.0	2.6 ± 4.1	0.999
Movement time (min)	11.7 ± 11.1	14.8 ± 13.4	0.942
Saturation artefact (%)	7.3 ± 14.4	8.5 ± 14.3	0.995

5.4.2 Agreement between AcuPebble SA100 and gold standard multi-channel sleep study.

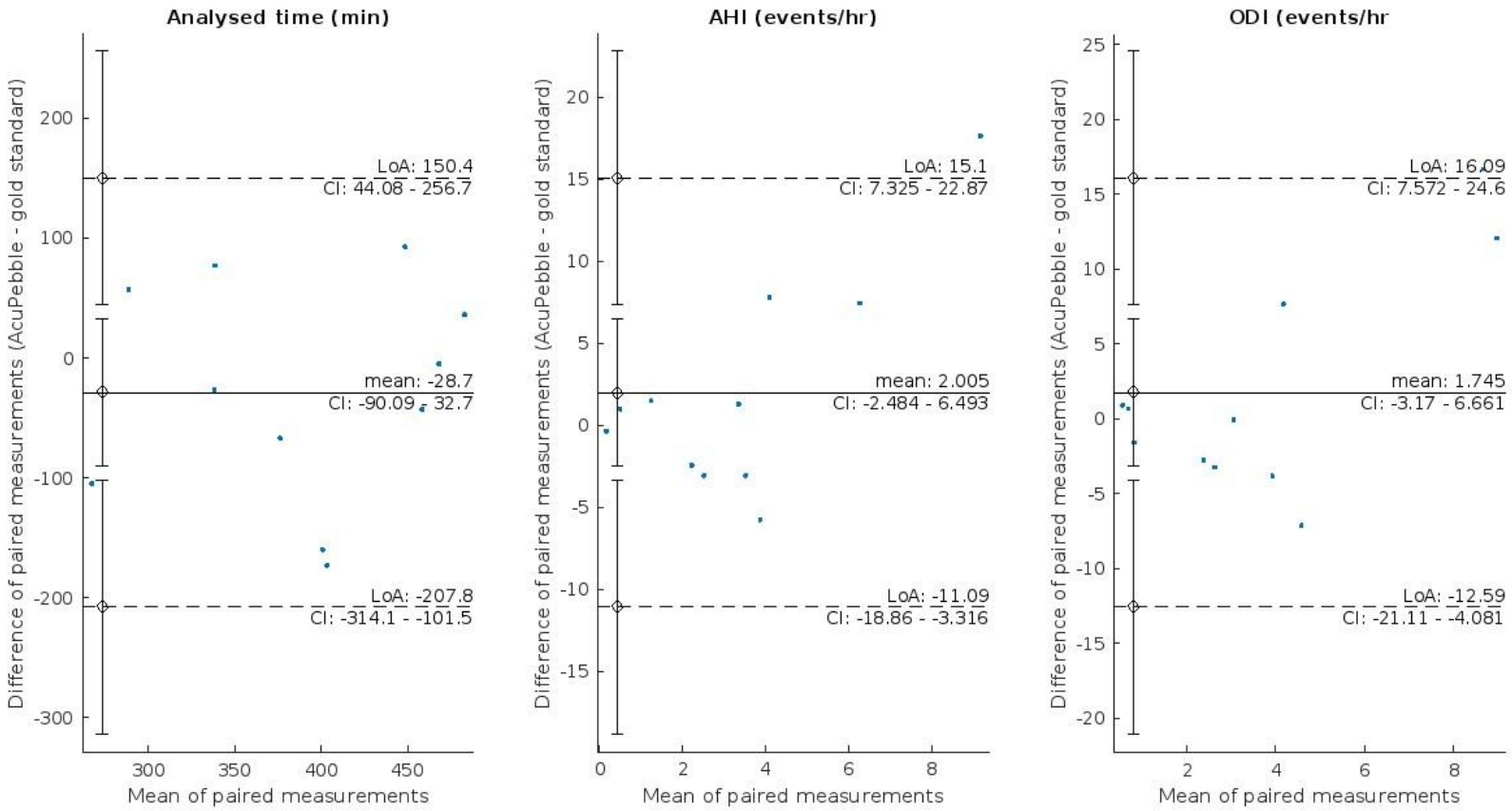
A total of 11 studies had concurrent AcuPebble SA100 and multi-channel sleep study from nine participants. The remainder had poor AcuPebble SA100

recordings or poor multi-channel sleep study data and so were excluded from the analysis.

While the recorded start and stop times of AcuPebble SA100 are based on when participants press ‘start’ and ‘stop’ on the accompanying mobile phone application, they may not be representative of the actual time asleep. AcuPebble algorithms can estimate the actual sleep duration, which may be different from when participants press ‘start’ and ‘stop’, and this is used as the analysis time.

The Bland-Altman plots comparing the analysed time, AHI and ODI between AcuPebble SA100 and the gold standard multi-channel sleep study are shown in Figure 5-3. The mean difference (95%CI) and therefore bias between all three measures was clinically significant, [analysed time: -28.7mins (-90.09 – 32.7), AHI: 2.005 events/hr (-2.484 – 6.493), ODI: 1.745 (-3.17 – 6.661). The limits of agreement were each were also very wide and clinically significant.

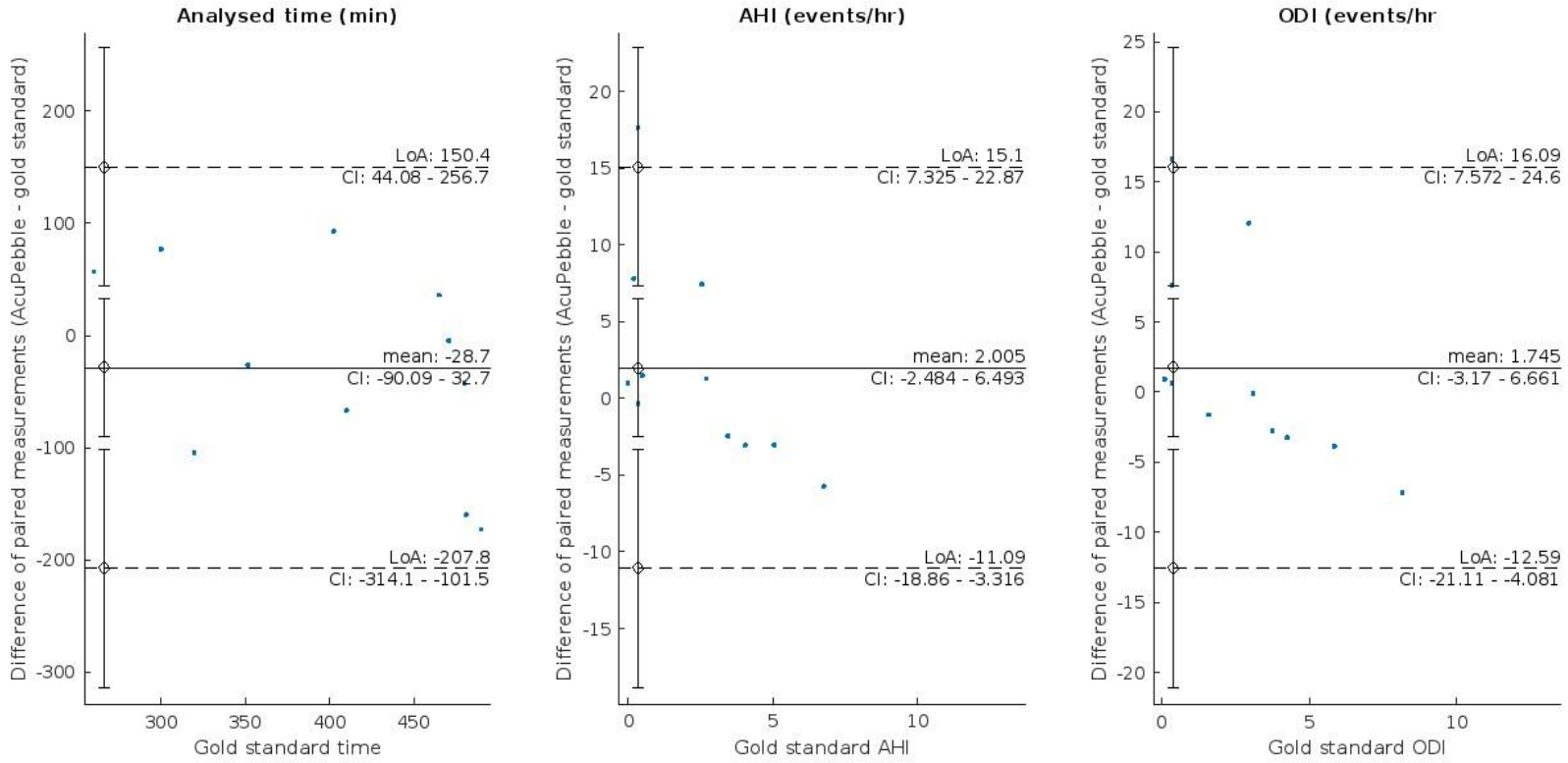
Figure 5-2 Bland-Altman plots comparing AcuPebble SA100 with gold-standard multi-channel sleep studies (n = 11)



While the numbers were too small to fully appreciate any trends in the data, to assess whether AcuPebble SA100's performance varied depending on the residual AHI, further Bland-Altman plots were constructed by plotting the difference of paired means against the gold standard AHI as first shown by Krouwer et al. (303) This was used to assess trend, given the significant fluctuations present in AcuPebble SA100 recordings which would give rise to bias in assessing trends, if the mean of paired measurements were used as above.

These plots (Figure 5-4) showed that, for higher AHI and ODI values, indicative of more severe disease, AcuPebble SA100 under-called these events, resulting in a more negative mean difference observed.

Figure 5-3 Bland-Altman plots comparing AcuPebble SA100 with gold-standard multi-channel sleep studies using the gold-standard as the x-axis (n = 11)

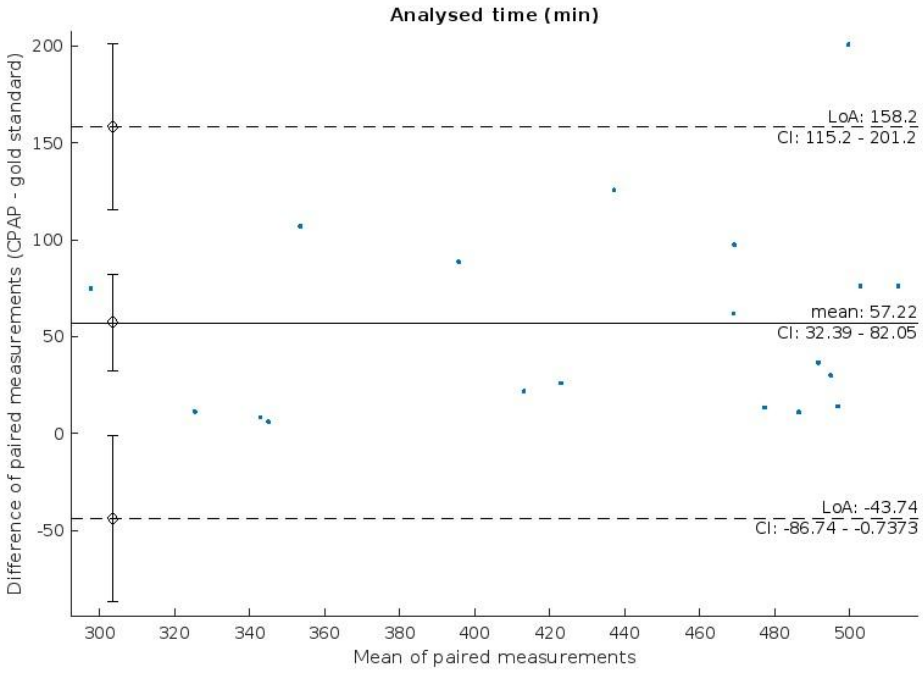


5.4.3 Agreement between CPAP machine and gold standard multi-channel sleep study

A total of 19 studies from 11 participants were available to compare parameters derived from CPAP machine and the gold standard sleep study. Three studies were performed on Lowenstein CPAP devices and the remainder were Philips CPAP devices. Participants used the CPAP machine for a mean (SD) duration of 7 hours and 42 minutes (1 hour and 18 minutes), with average pressure requirements of 8.52cmH_2O (2.07) and an average leak of 14% (18%).

While the start and stop times were matched as closely as possible, this was not possible in all the studies, due to the CPAP device starting either before the sleep study or finishing afterwards. This led to a time discrepancy in 11/19 studies, where there was more than a 30-minute time difference. Moreover, three studies were performed on a Lowenstein CPAP device, for which the machine data does not give the exact start and stop time, thus estimation of this time was performed based on visual inspection of the graphical data. It is also worth noting that even if the start and stop times matched exactly, the analysed time for the multi-channel sleep study could differ as periods of movement or artefact were removed prior to analysis as is the convention. The Bland-Altman plot for the analysed time can be seen in Figure 5-5. The mean time difference and therefore bias was 57.22mins (32.39 – 82.05). This meant that on average the CPAP machine analysed an extra 1 hour of time compared to the gold standard measure. There were also wide limits of agreement as shown in Figure 5-5.

Figure 5-4 Bland-Altman plot comparing CPAP and gold-standard analysis time.



Bland-Altman plots comparing the overall AHI, obstructive apnoea, obstructive hypopnea between the CPAP machine and the gold-standard multi-channel sleep study can be seen in Figure 5-6. The mean difference (95%CI) and therefore bias in these parameters was unlikely to be of clinical significance [overall AHI: 1.46 (0.56 – 2.37), obstructive apnoea: 0.29 (-0.09 – 0.67), obstructive hypopnoea: 1.04 (0.18 – 1.9)]. However, the overall AHI and the obstructive hypopnoea parameters did have a high upper limit of agreement (overall AHI: 5.13 (3.57 – 6.69) and obstructive hypopnoea: 4.54 (3.05 – 6.03)), which may be of clinical significance.

Trends were difficult to appreciate in this data, even when using the gold-standard AHI on the x-axis (Figure 5-7).

Figure 5-5 Bland-Altman plots comparing CPAP with gold-standard multi-channel sleep studies (n = 19)

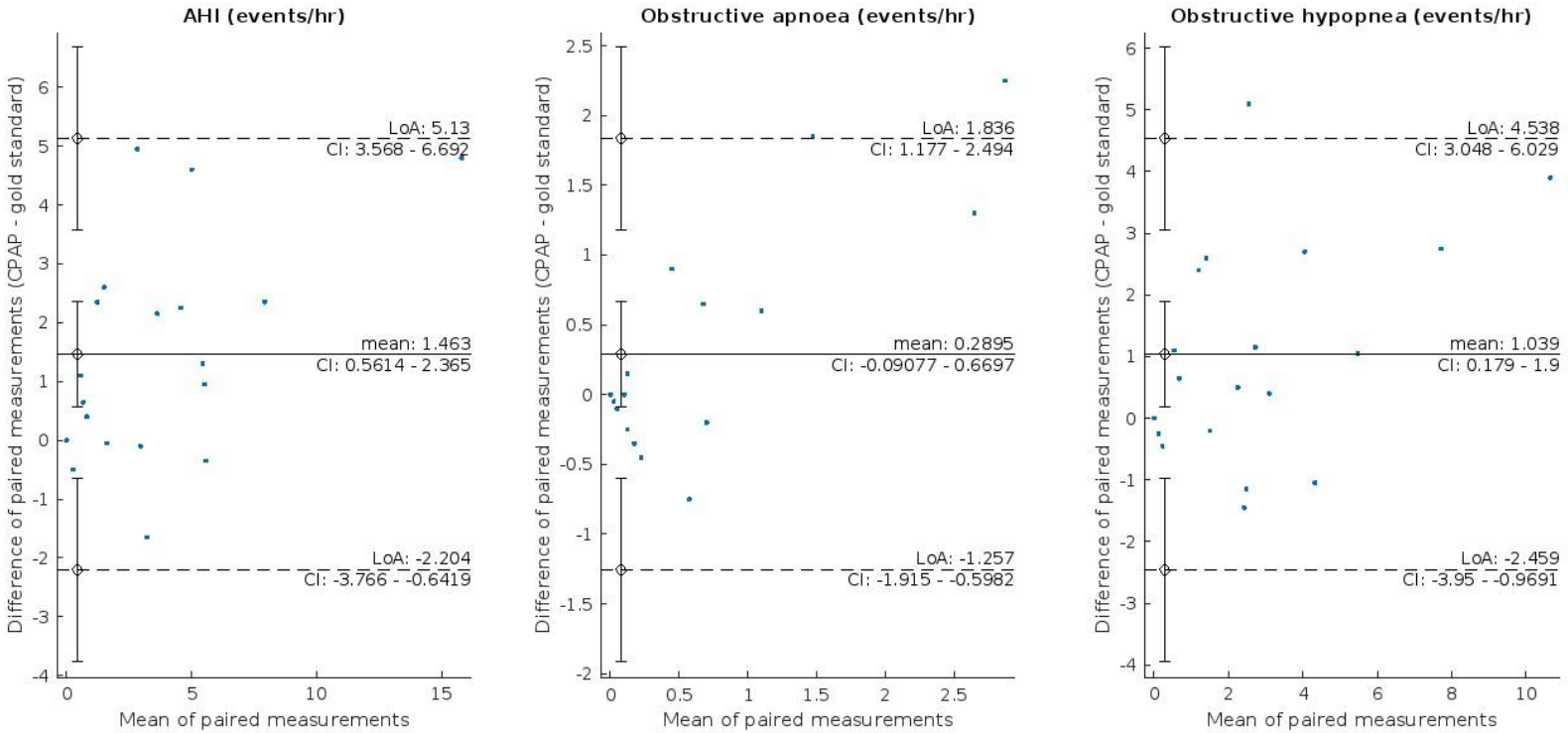
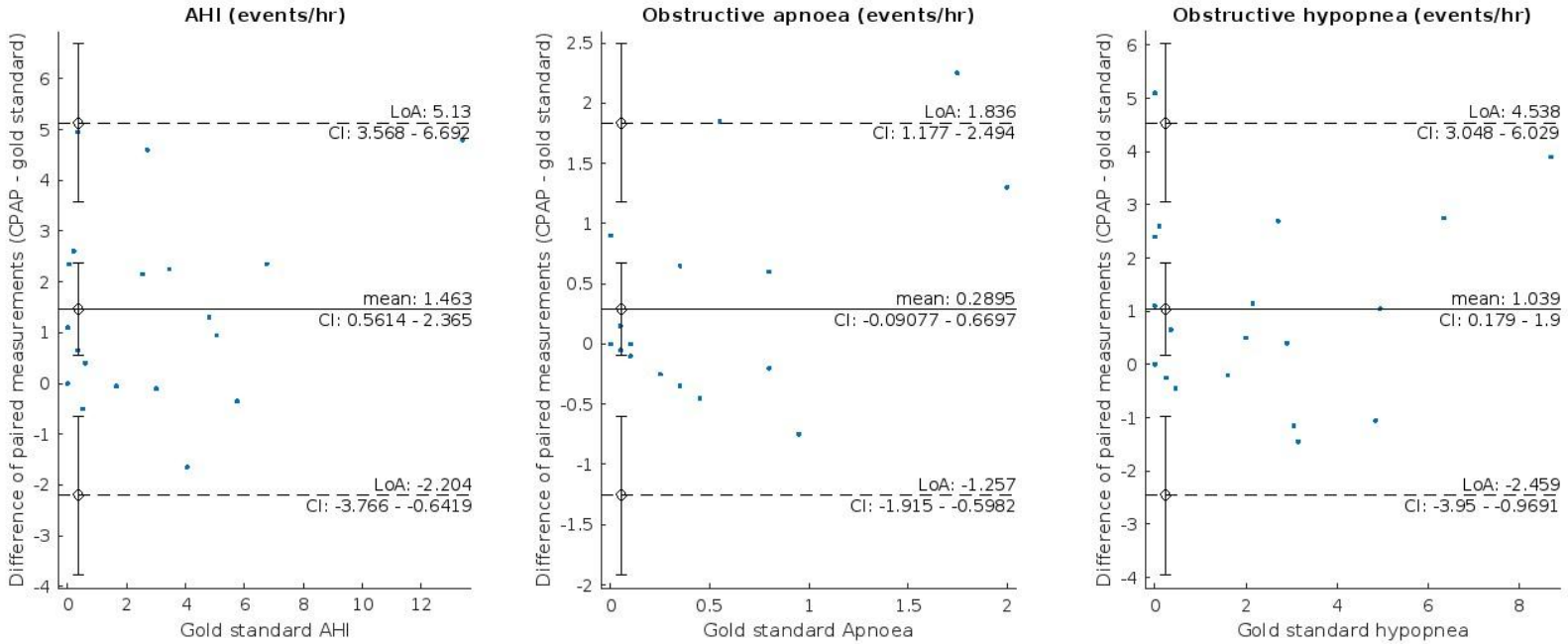


Figure 5-6 Bland-Altman plots comparing CPAP with gold-standard multi-channel sleep studies using the gold-standard as the x-axis (n = 19)



While the overall number of sleep studies were small, a sensitivity analysis was performed to assess whether the device type, leak of more than 15%, and closer analysed time matching made a difference to the overall bias. This can be seen in Table 5-4.

With regards to distinguishing between the residual and effective AHI, only 2/19 studies had an extra hour of analysis available once CPAP had finished, thus giving the effective AHI. Due to the small number, and only one extra hour available, it was not possible to assess differences between the residual and effective AHI.

Given the inaccuracies observed with AcuPebble SA100 in detecting the residual AHI, it was not possible to directly compare AcuPebble SA100 and CPAP residual events.

Table 5-4 Sensitivity analysis when comparing CPAP derived measures from the gold standard sleep study.

Subgroup	Recording time (min)			Overall AHI			Obstructive Apnoea			Obstructive hypopnea		
	Mean bias (95% CI)	**Upper LOA (95% CI)**	**Lower LOA (95% CI)**	**Mean bias (95% CI)**	**Upper LOA (95% CI)**	**Lower LOA (95% CI)**	**Mean bias (95% CI)**	**Upper LOA (95% CI)**	**Lower LOA (95% CI)**	**Mean bias (95% CI)**	**Upper LOA (95% CI)**	**Lower LOA (95% CI)**
Device Type												
Philips (n = 16)	59 (-29 –87)	168 (117 – 219)	-49 (-101 – 2)	1.7 (0.7–2.7)	5.5 (3.7 – 7.3)	-2.1 (-3.9– -0.3)	0.4 (-0.1–0.8)	2.0 (1.2 – 2.8)	-1.3 (-2.1– -0.5)	1.2 (0.3– 2.2)	4.9 (3.2 – 6.6)	-2.4 (-4.2– -0.7)
Lowenstein (n = 3)	47 (-13 – 107)	94 (-9 –198)	0 (-104 – 103)	0.2 (-1.3– 1.7)	1.4 (-1.2 – 4.0)	-1.0 (-3.6 – 1.6)	-0.1 (-0.4 – 0.2)	0.2 (-0.4 – 0.7)	-0.4 (-0.9– 0.2)	0.0 (-1.4– 1.4)	1.1 (-1.3 – 3.7)	-1.2 (-3.7– 1.4)
Leak												
<15% leak (n = 12)	58 (-35 –82)	133 (91 –174)	-15 (-57 – 26)	1.2 (-0.1 – 2.5)	5.2 (2.9 – 7.5)	-2.9 (-5.2 - -0.6	0.4 (-0.2 – 1.0)	2.2 (1.2 – 3.2)	-1.5 (-2.5 - -0.4	0.7 (-0.6 – 2.0)	4.7 (2.5 – 7.0)	-3.3 (-5.6 - -1.1
>15%leak (n = 7)	55 (-13 – 122)	198 (80 – 315)	-88 (-205 – 28)	2.0 (-0.6 – 3.3)	4.9 (2.5 – 7.2)	-0.9 (-3.3 - 1.4	0.1 (-0.3 – 0.6)	1.1 (0.3 – 1.8)	-0.8 (-1.5 - 0.0	1.6 (-0.6 – 2.6)	3.7 (2.0 – 5.4)	-0.5 (-2.2 - 1.2
Start / stop time difference												
< 30-minute difference (n = 8)	14 (8 – 19)	27 (17 – 37)	0.1 (-8 – 11)	0.9 (-0.3 – 2.2)	3.8 (1.7 – 6.0)	-2.0 (-4.2 – 0.2)	0.3 (-0.4 – 1.1)	2.0 (0.8 – 3.3)	-1.3 (-2.6 – -0.1)	0.5 (-0.9 – 1.9)	3.7 (1.3 – 6.1)	-2.8 (-5.2 – -0.4)
> 30-minute difference (n = 11)	88 (57 – 120)	180 (126 – 234)	-2.7 (-57 – 52)	1.9 (0.5 – 3.3)	5.9 (3.5 – 8.4)	-2.2 (-4.6 – 0.2)	0.25 (-0.3 – 0.8)	1.8 (0.9 – 2.7)	-1.3 (-2.2 – -0.4)	1.4 (0.2 – 2.6)	5.0 (2.9 – 7.2)	-2.2 (-4.3 – 0)

5.4.4 Usability of AcuPebble SA100

Usability feedback was obtained from 10/17 participants. Half (5/10) of the participants found the AcuPebble SA100 device easy or very easy to attach, with 4 finding it moderately easy and 1 participant found it very difficult. Participants struggled with attaching the app to the sensor, with 2/9 finding it difficult, 3/9 moderately easy and 4/9 finding it easy. The majority (7/10) found the sensor at least moderately comfortable, and found the sensor remained in place for both nights of the study (9/10).

Some participants commented that the device was difficult to charge and there were some issues connecting the sensor to the mobile phone application. Others found the set up easy and found no issues with the study overall.

5.5 Discussion

The data from this observation study has shown:

1) AcuPebble SA100 in its current format cannot accurately determine the residual AHI in patients with OSA on CPAP therapy.
2) CPAP machines seemed more accurate than AcuPebble SA100 in determining the residual AHI in patients with OSA on CPAP therapy, given the better overall mean bias and limits of agreement when compared to gold standard. Head-to-head comparisons could not be made in this study due to the observed inaccuracies with AcuPebble SA100. However, the upper limit of agreement when comparing CPAP vs. gold standard for the overall AHI is likely to be clinically significantly different.
3) Participants generally found the sensor moderately comfortable and moderately easy to attach and use, but some struggled connecting the sensor to the mobile phone application.

This study recruited mainly male participants with primarily severe OSA (median AHI 54.5 (33 – 75.8) who were concordant with CPAP use (mean nightly CPAP ~ 7 hours (±1 hour)). Participants were not somnolent with a median Epworth sleepiness score of 4 (3-11) and had a reduced baseline symptom burden. The mean subjective duration of sleep was 7 hours (± 0.7hours), which largely matched CPAP use, meaning that this population in the main used CPAP for the entire duration of their sleep. This meant that differences between the residual and effective AHI could not be appreciated. This was therefore a population who were not symptomatic and had well controlled OSA (mean (SD) AHI on CPAP across all studies 2.9 (3.4)). From the 19 consented participants only 11 had adequate multi-channel sleep study data, resulting in 19 possible sleep studies that could be analysed.

Gold standard multi-channel sleep studies were scored by two independent researchers with adequate training based on the AASM criteria (304) and a ≥4% oxygen desaturation threshold. There was very good interrater reliability with the overall AHI having an ICC of 0.984. This is similar to previously published literature. (305, 306) While the ICC of the obstructive events appeared lower at 0.532, the actual mean and SD values between both scorers fell within a clinically accepted difference range of less than 1 event/hour.

There was poor overall agreement between AcuPebble SA100 and the gold-standard multi-channels sleep study data. While the mean AHI bias (95%CI) may be clinically acceptable (2 events/hr (-2 – 6)), there were wide limits of agreement with an upper limit of 15 events/hr and lower of -11 events/hr, suggesting the device is not reliable in detecting the residual AHI in patients undergoing CPAP therapy. Furthermore, when the gold standard was used as the x-axis of the Bland-Altman plot, there was a suggestion of a negative AHI and ODI trend, meaning that for a higher residual AHI

(as shown by the multi-channel sleep study), AcuPebble SA100 under-called these events, resulting in a more negative bias. This is clinically significant, as AcuPebble SA100 may under-represent a patient's disease severity, leading to false reassurance and a lack of further investigation. While these findings must be interpreted with a degree of caution given the high degree of attrition bias, with only 11/34 studies having acceptable and comparable data, it is likely that AcuPebble SA100 in its current format cannot be used to monitor.

AcuPebble SA100 has previously been shown to have a high positive (96%) and negative (99%) predictive value in diagnosing OSA. (145) There are two potential reasons which may explain the inaccuracy observed in this study. Firstly, AcuPebble SA100 is an acoustic device that detects sound from the airway and converts this through various algorithms into the AHI and ODI based on the AASM recommendation. Patients on CPAP therapy are likely to have a large degree of external noise interference from the machine itself, which is likely to interfere with the device algorithms, and may account for some of the differences seen. Secondly, the analysed time from AcuPebble SA100 and the multi-channel sleep study differed significantly, this therefore may affect the actual AHI which is reported as events/hr. If the denominator differs, the actual value will too.

There is a paucity of data looking at the role of wearables in determining the residual AHI in patients on CPAP therapy. Epstein et al (301) showed concluded that in patients suspected to have poor controlled OSA, a home sleep apnoea testing kit (WatchPat®200) performed better than the CPAP machine in nearly 50% of this population. However, a key limitation to this study was no gold-standard comparator arm, and thus an assumption that WatchPat®200 accurately diagnoses the residual AHI while patients are using CPAP therapy. Other novel wearable devices that have

been investigated to diagnose OSA, have not yet been tested to monitor residual sleep events while on CPAP.

Our study showed an acceptable agreement between the CPAP machine and gold-standard sleep study with a mean bias of 1.5 events/hr (0.6 – 2.4). However, the upper limit of agreement was still too high (5.1 events/hr (3.6 – 6.7)), while the lower limit of agreement was clinically acceptable (-2.2 events/hr (-3.8 – -0.6). The CPAP machine was more accurate when it came to detecting the residual obstructive apnoea events compared to the hypopnoea events. This data suggests that CPAP machines may detect higher than actual residual AHI events, especially if the residual events are hypopnoea's compared to apnoea events, leading to a higher number of subsequent and potentially unnecessary investigations.

While our data is similar to previously published data, differing CPAP devices provide different biases and limits of agreement when compared to gold standard polysomnography. (298, 307-310) In the main, studies have found detection of hypopnoeas to be more problematic and less accurate than apnoea detection when compared to gold standard. A summary of some of the prior data can be seen in Table 5-5.

While we had a small number of studies, sensitivity analyses suggested a lower leak percentage resulted in less overall AHI and hypopnea detection bias compared to a higher leak percentage > 15%. This study also showed that CPAP had a significantly different analysed time bias of 57 mins, which may also affect the results. Sensitivity analyses suggested improved diagnostic accuracy when there was a less than 30minute difference in analysed times compared to more than 30 minutes (mean bias 0.9 vs. 1.9).

Usability feedback was only returned in 10 patients who in the main found AcuPebble SA100 easy to use and attach, with most finding it moderately comfortable. However, they were problems with regards to application-to-sensor connectivity that needs improvement in future iterations. This significantly differs from a prior study investigating the diagnostic accuracy of AcuPebble SA100, where 99% felt confident using the mobile phone application and comfort levels were a lot higher. (145) There may be an element of recall bias in our work, as participants had to wear three devices (CPAP, AcuPebble SA100 and a multi-channel sleep study). The combination of three devices may have led to decreased perceived comfort of the device itself. Nonetheless, further work needs to be done to assess whether there is widespread acceptability of the device.

Table 5-5 Prior work comparing CPAP derived measurements to gold standard multi-channel sleep studies.

Author and device tested (n)	Overall AHI			Apnoea events			Hypopnoea events		
	Mean bias	Upper LOA	Lower LOA	Mean bias	Upper LOA	Lower LOA	Mean bias	Upper LOA	Lower LOA
Ueno et al (2010) S8 Auto-CPAP device, ResMed (n = 70) (298)	-5.7	0.1	-11.5	-0.5	1.3	-2.3	-5.3	0.1	-10.7
Cilli et al (2012) (REMstar Auto) (n = 137) (307)	0.05	4.9	-4.8	-	-	-	-	-	-
Nigro et al (2015) S9 Autoset, ResMed (n = 114) (310)	-3.5	4.2	-11.2	-	-	-	-4	4.1	-12.1
Fanfulla et al (2021) Various devices* (n = 299) (308)	-2.42	9.16	-14	While the Bland-Altman plot was not presented. The median gold standard index was 2.8 ± 5.3 vs. machine 2.9 ± 5.6.			While the Bland-Altman plot was not presented. The median gold standard index was 4 ± 6 vs. machine 1.5 ± 2.3, p<0.001		
Foresi et al (2023) AirSense 10 ResMed (n = 41) (309)	0.57	4.5	-3.3	-	-	-	-	-	-
Our study data Philips and Lowenstein devices (n = 19)	1.5	5.1	-2.2	0.3	1.8	-1.3	1.0	4.5	-2.5

* This study used a variety of positive airway pressure devices in a real-life study. 53% were on CPAP and the other's were on differing modes of ventilation

There are several notable limitations to this work. First, the study had a high attrition bias, with many multi-channel sleep studies not being suitable for analysis. This is lower than previously reported home based sleep study failure rate, with one prior study reporting only a 4% failure rate. (311) However, it is probable, that the additional use of CPAP while conducting a home-based sleep study is likely to have resulted in a higher failure rate. Other comparative work in the literature has often used in-lab sleep studies and so cannot be compared to this work. Second, because of poor-quality data, the study was under-powered. A truly powered study may reduce the limits of agreement observed with AcuPebble SA100 and may suggest that the device is clinically usable. However, device adjustments, to account for the extra noise from the CPAP machine, are likely to lead to more accurate results and should be performed prior to conducting a larger trial. Moreover, true differences between CPAP and gold standard measures may not also be realised. Third, participants had well controlled OSA, meaning that the ability of both CPAP devices and AcuPebble SA100 to detect higher residual AHI was not adequately tested. This is important, as this is often where the devices have the most clinical utility, given these are the patients with likely ongoing symptoms. Fourth, we were unable to detect differences between the residual and effective AHI, given the lack of data. This work remains important clinically and needs consideration for future larger studies.

In conclusion, this small observational study has shown that AcuPebble SA100 in its current form is not accurate in determining the residual AHI in patients with OSA on CPAP therapy. While the CPAP machines used in this study appear more accurate, they had a wide limit of agreement and are likely

to overscore hypopnoea events. Prior existing studies have suggested that different CPAP machines have varying accuracies in detecting the residual AHI, a finding that has also been noted by the American Thoracic Society, (74) and therefore their use in clinical practice needs caution. Given different centres use different machines, each sleep service should conduct a study sampling their own machine accuracy to ensure clinical reliability and use. However, future wearables need to be designed and tested to accurately and easily determine the residual AHI on CPAP therapy, so that patients can be better monitored irrespective of machine brand.

The previous chapters have described four studies conducted for this thesis. The next chapter provides an overall discussion and also discusses ideas for future work, building on this thesis.

CHAPTER 6

6. Chapter 6 – Discussion

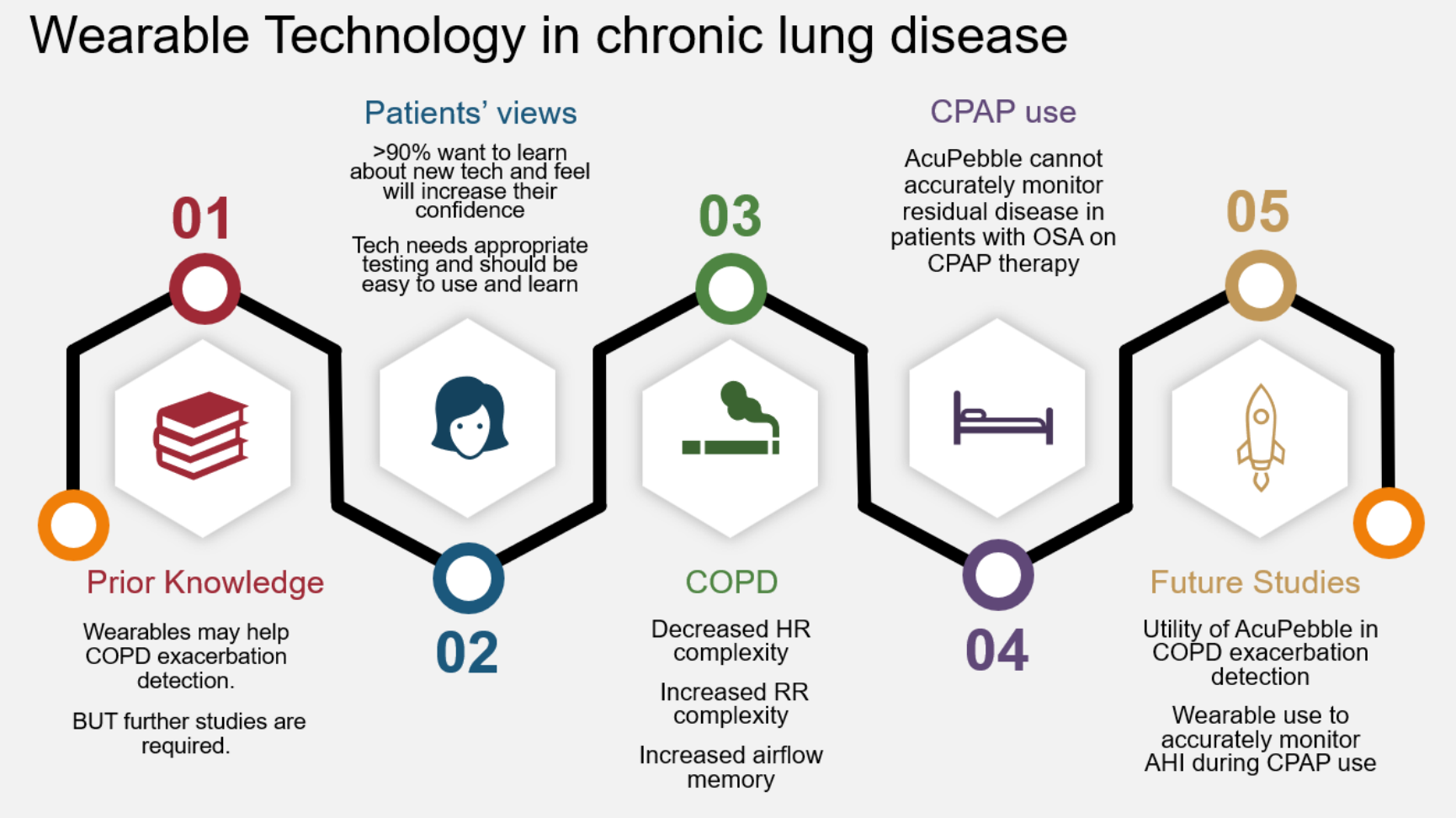
Wearable technology is set to grow exponentially in the next decade, with an estimated market value of $195.57 billion by 2027, (92) and the world health organisation has recognised a shift to digital healthcare. (93) Therefore, the role of wearable technology in chronic lung disease is of paramount importance. Wearables have the ability to improve patient self-management, decrease health burden and reduce patient morbidity and mortality. Therefore, research into novel wearable devices is critical, to not only help identify potential uses, but to also gauge acceptability. This in turn will help new devices become clinically useful and acceptability and make a difference to patients in real terms.

During my research, I sought to:

1. Understand and summarise the current role of wearable technology in COPD management.
2. Explore the acceptability of wearable technology in a group of patients with chronic respiratory disease.
3. Determine whether there were any differences in continuous physiological measurements in stable COPD patients and those undergoing an exacerbation.
4. Determine the accuracy of wearable technology in monitoring patients undergoing CPAP treatment for sleep apnoea.

A summary infographic and results from this thesis can be seen in Figure 6-1.

Figure 6-1 Wearable technology in chronic lung disease



6.1 Understanding the current landscape of wearable technology in COPD management.

To date, I have found that there has been a large body of work looking at the role of step-counters / pedometers to improve physical activity metrics in patients with COPD, specifically mean daily step count and the six-minute walk distance. For the most part, these improvements are short-lived and have little impact on quality-of-life measures and exacerbation rates. However, it seems clear that when step-counters are used as part of a multi-faceted approach, there appears to be greater gains in step-count improvement.

No study has investigated the role of other wearable devices to improve physical activity, capacity or intensity. This is an area that needs further research and development.

With respect to exacerbation detection, there have been few studies that have shown promising application of continuous physiological monitoring using wearables to predict exacerbations. However, one of these studies only included 13 patients and had a high attrition rate, (188) and the other combined wearables with environmental measurements which can be costly and cumbersome to replicate in a real-world setting. (193) Further studies in this field are clearly essential to improve patient outcomes. Early identification of a COPD exacerbation has been listed as key unmet clinical need by the National Institute for Health and Care Research (NIHR) and wearable technology has the potential to fill this need. (35)

The first step in realising this potential is to use a simple wearable device to identify key physiological differences that exist between stable COPD patients and those undergoing an exacerbation. The second would be to follow a group of COPD patients for a prolonged period, to capture five phases: stability, pre-exacerbation, exacerbation, post-exacerbation, recovery to stability. The third step would be to create an algorithm whereby patients use the wearable device to measure regular physiological measurements and receive an alert to say an exacerbation is likely, resulting in early intervention including medication review and avoidance of a severe exacerbation necessitating hospital admission. This would likely lead to quicker recovery back to the stable state.

It is important to note, that simply designing and developing a wearable device that could detect a COPD exacerbation is not enough, if patient uptake, acceptance and compliance is lacking. Through my survey, I have shown that people living with chronic respiratory diseases are likely to be agreeable to learn about novel technology, feel that it will increase their confidence in monitoring their condition, and aid self-management. This positive attitude towards new technology is important as this is a key metric in understanding whether a certain population will be receptive to the technology and thus accept and use it.

Participants wanted a product that was accurate, easy to learn, easy to use, approved by regulatory bodies following rigorous testing, with less emphasis on aesthetics and data privacy. Importantly they wanted a device to link to their

own mobile phone, thus giving them real time information. In the primarily white British population surveyed, social norms were less important in driving acceptance. It is also worth noting that most participants had low-middle income earnings, meaning any new technology would have to be affordable to increase reach and equity.

The current landscape of wearable technology in COPD is promising. Future work needs to focus on designing simple to use wearable devices that are accurate and affordable, easy to learn and use, which aid exacerbation detection and symptom management. This will empower patients to self-manage their condition, ease the pressure on a busy national health service and improve patient morbidity and possibly mortality.

6.2 Measurable differences between stable and exacerbating COPD patients using a novel wearable device AcuPebble RE100.

A simple wearable device, AcuPebble RE100, was able to continuously measure patients' respiratory rate (RR), heart rate (HR) and airflow and was acceptable to most participants. However, the device had some notable limitations. Firstly, stable COPD participants only used the device for 60% of the prescribed duration (median 18 nights (10 – 26)). Second, a high rate of attrition was found in those undergoing an exacerbation, especially post discharge, with only 50% of participants having data 5 days post discharge. Third, HR and airflow data capture had significant artefact meaning a large number of recordings could not be analysed. Fourth, whilst the mean HR data from AcuPebble RE100 was accurate, variability and complexity

measurements were less accurate. This is likely due to the filtering algorithms applied during the recording.

These limitations from the device can be improved upon in future iterations. The limited battery life and prolonged upload time of the data from device to a GDPR compliant cloud, was a hindrance and made it slightly cumbersome for patients and may be partly responsible for the high attrition rate. Other reasons are likely to be technology acceptance and confidence. While our survey showed this age group of patients with chronic respiratory disease are agreeable to technology in the main, during a period of sickness, the added effort to use technology may add an unnecessary burden. To encourage participants to use future wearables more consistently, work needs to be done in conjunction with national charities like Asthma and Lung UK, to promote the benefits of the technology.

AcuPebble RE100 generated a large amount of data points for each patient and thus the usual static analysis methodologies commonly used in medical research like mean, median and standard deviation was not enough to summate the data and detect differences. While techniques for variability and complexity analysis have been around for a while, their use has not yet been clinically normalised. Furthermore, there is a paucity of data specifically relating to respiratory rate and airflow. This is likely to be in part due to the lack of wearables that can accurately collect this information. This study allowed exploration of various variability techniques and the use of sample entropy to

assess time-series complexity, to understand differences between stability and exacerbation.

While the HR variability and complexity data was less accurate due to noise interference, differences still existed between stable COPD participants and exacerbators. This means that future algorithms can be built based on the differences found. Moreover, multi-scale entropy, which is more robust to missing data also showed significant differences. This means HR measures can still be incorporated into future algorithms to detect the start of an exacerbation. However, it is important to note, that a high degree of artefact, means that participants are likely to need a longer and more frequent recording period (e.g., use every day compared to every other day).

The device found significant differences between a stable COPD population and one undergoing an exacerbation. HR variability increased during an exacerbation, while complexity decreased. RR variability and complexity both increased during an exacerbation and at longer scales (above 30 seconds), exacerbators had a significantly lower airflow α3 value compared to stable patients, suggesting the airflow was more random during an exacerbation compared to the stable state. While some of these trends 'reversed' or went back towards the stable state during the recovery period following an exacerbation, small numbers in this study, make firm conclusions difficult.

It is perhaps unsurprising that differences in common physiological measures exist between these two patient groups of patients. However, importantly, these differences only became apparent when non-routine analysis methods

were employed. The mean HR and mean RR measures did not significantly differ between the groups, highlighting the need for the development and optimisation of more complex analysis methods.

6.3 The accuracy of wearable technology in monitoring patients undergoing CPAP treatment for sleep apnoea.

AcuPebble SA100 is used clinically as a medical diagnostic device for OSA with a high positive and negative predictive value when compared to gold standard sleep studies. However, this device was not reliable in detecting residual disease severity, as measured by the apnoea/hypopnoea index (AHI) in patients undergoing treatment with continuous positive airway pressure (CPAP) therapy. Bland-Altman analysis showed a high bias and wide limits of agreement. This is likely to be due to the significant noise interference from the CPAP machine on this acoustic wearable device, meaning that future iterations require algorithm manipulation to improve accuracy. The CPAP machines in our study were better at detecting the residual AHI (with a lower bias and reduced limit of agreement) when compared to gold standard multi-channel sleep studies. However, we only tested participants who already had good concordance and relatively good disease control. Existing literature points to inaccuracies with CPAP machines detecting residual events in this patient population, and therefore, further work needs to be done to find a simple solution to monitor this patient group, such that treatment effectiveness can be appropriately and simply measured.

6.4 Future work

Work in the future needs to expand upon the completed work in this thesis. It is clearly evident from the systematic review, that further studies investigating whether other physical activity metrics including movement intensity and exercise capacity can be improved in the long term by using wearable technology in addition to other facets. Further work into other aspects of COPD management needs to be investigated. For example, the role of wearables in promoting and helping with smoking cessation, improving attendance at pulmonary rehabilitation, maintaining pulmonary rehabilitation post classes and inhaled therapy.

From the main study, we have clearly shown AcuPebble RE100 has the potential to differentiate between stable and exacerbating patients, but this needs further work. The following section describes two potential future studies to expand on the work on this thesis.

6.4.1 Observational study using AcuPebble RE100 in a group of stable COPD patients

This study would aim to give AcuPebble RE100 to a group of stable COPD patients over a 1-year period. Participants would wear the device every night for a year and the same physiological measures (heart rate, respiratory rate and airflow) would be collected. Alongside the device participants would fill in a symptom diary which aims to understand their symptom burden daily. During this period, participants are likely to go through various phases of their disease including:

a) Stability
b) Pre-exacerbation phase
c) Exacerbation
d) Early recovery
e) Stability

By analysing physiological parameters using linear and non-linear analysis methodology, differences between these phases can be identified. This can be compared with subjective symptom burden. This will enable us to identify whether physiological changes occur prior to a perceived increase in symptom burden and how quickly these changes return to normal. It will also give us an understanding of how management of these exacerbations affects the overall trajectory. The main objective behind this study would be to develop an algorithm whereby AcuPebble RE100 can automatically detect an upcoming exacerbation prior to symptom onset and 'warn' patients such that earlier action could be taken. AI and machine learning could be used such that the algorithms get more specific and accurate every year. This could be investigated in the next study as described below.

6.4.2 Randomised controlled trial using AcuPebble RE100 to allow earlier identification and treatment of a COPD exacerbation.

This study would aim to randomise COPD patients to receive either AcuPebble RE100 to wear nocturnally over a one-year period or usual care. Participants in the AcuPebble RE100 group would get a warning when an upcoming exacerbation is detected by the device and be advised to commence on oral

steroid treatment for five days, as this is current standard practice. Participants in the usual care group would only take oral steroids when they subjectively feel they are undergoing an exacerbation or when their healthcare practitioner feels they are having an exacerbation. The primary outcome of interest would be the number of hospitalisations / hospital attendances for a COPD exacerbation over the course of the study period. The primary safety outcome of interest would be the number of steroid courses received over the course of the study period. The PICO model / approach is shown below:

- P – the population being studied is a group of stable COPD participants
    - COPD will be defined as post-bronchodilator spirometry showing an FEV1/FVC ratio of <0.7 combined with an at least 10-pack year smoking history.
    - Stability will be defined as no exacerbations in the last 3 months
- I – the intervention of interest in this case with be AcuPebble RE100
    - All participants in this group will receive AcuPebble RE100. They will wear this nocturnally for the study period. A warning will be delivered via an accompanying mobile phone application which tells them that an exacerbation is likely to occur soon. They will be then advised to start a 5-day course of oral steroids.
- C – the control group will be usual care.
    - They will not receive a device and will simply be monitored remotely to assess they exacerbation status and medication use.
    - They will engage in filling out a daily symptom diary

- O – the primary outcome of interest would be the number of hospitalisations / hospital attendances for a COPD exacerbation over the course of the study period. The primary safety outcome will be the number of steroid courses taken during the course of the study period. Secondary outcomes would include cost-effectiveness measures.

6.4.3 AcuPebble SA100 and residual events in patients using CPAP therapy.

The currently used AcuPebble SA100, needs further modification prior to re-trialling its ability to detect residual events in the OSA population undergoing CPAP therapy. CPAP machines are inaccurate to reliably understand the disease burden in concordant but symptomatic individuals and further work needs to be done in this field to provide a simple solution for patients.

6.4.4 Future wearables and signal interpretation

Finally, it is worth noting that future wearables will enable clinicians and researchers to gather a large quantity of continuous physiological measurements and work needs to be done to try and understand how to interpret these signals such that they have clinical utility. Heart rate variability and complexity analysis has been evolving for over 20 years but its place and routine use in clinical practice has not yet been established. This is likely to be due to a myriad of different approaches, analysis methods and a lack of available continuous data in routine clinical practice. Furthermore, there is no standardisation of these techniques and no easily available normal ranges, such that this can be incorporated into meaningful clinical practice. (312) This

is even more so for other physiological measures like respiratory rate and airflow.

The human body consists of a complex interplay of signalling pathways which all interact and interfere with one another. This complex physiological network map needs further investigation and may hold the key to assess the transition from stability to instability, such that flare-ups or exacerbations of otherwise stable chronic diseases can be recognised and acted upon.

As a first step, building a repository / database of nocturnal physiological signal variability measures for both healthy and diseased states is important. This can then lead to further specific research in different diseases.

6.5 Conclusion

The wearable technology landscape is fast evolving, but its utility in patients with chronic respiratory diseases, such as COPD and OSA needs further work. Acceptance and uptake of the technology is likely to be positive; however, the reliability and accuracy of this technology is still in its infancy. Nonetheless AcuPebble RE100, has been shown to be a simple, acceptable wearable device that can distinguish between COPD patients in a stable state and those undergoing a severe hospital exacerbation. Future work can build upon this to create a device that can predict an upcoming exacerbation thereby reducing patient morbidity and mortality and improve patient care for the better.

CHAPTER 7

7. Appendix

7.1 Appendix 1: Physiological signal variability

Physiological variability measures such as heart rate (HR) and respiratory rate (RR) are often summated by static, linear measurements like the mean and standard deviation. However, these measurements do not capture the variability and complexity of these signals that are occurring both in the short term (beat-to-beat) and long term. The human body represents a complex interplay of many different signalling pathways which impact each physiological variable in many ways. This complex interaction is often dynamic, non-linear, and ever-changing and physiological variability analysis can give useful information on the integrity of these control systems. (293)

To understand these concepts further, I have used the heart rate (HR) as an example of a complex physiological time series. A time series simply describes a collection of observations over time. For example, if a device measured the HR every two seconds over the course of six hours this would lead to 10,800 measurements. Simply using the mean and standard deviation in this instance would lose the subtle variations that exist amongst these data points. The HR and rhythm are continuously and dynamically regulated by the autonomic nervous system (ANS). The parasympathetic nervous system (PNS) slows the heart rate down by lengthening each R-R interval, (the interval between each successive heartbeat), and leads to an almost immediate reduction in HR due to a very short latency of the neurotransmitter acetylcholine. Therefore, the PNS regulates the HR on a beat-by-beat basis and accounts for the short-term

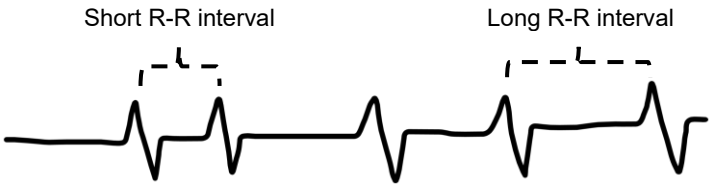
variability seen. The sympathetic nervous system (SNS) releases catecholamines and increase HR but has a slower onset and offset. It is important to note, that the PNS and SNS do not merely have opposite effects on the HR but rather have a complex interplay with often overlapping and different time frequencies of action. (245) Moreover, the ANS is not the only regulatory mechanism of HRV, but thermoregulation, respiration, baroreceptors and chemoreceptors all play a role in this complex system. (231) Therefore, capturing this variability and complexity is vital in understanding differences between different patient groups.

The next sections describe various linear and non-linear analysis methods used in this thesis, that aim to capture this variability and complexity.

7.1.1 Linear analysis measures

Successive R waves on an electrocardiogram (ECG) are denoted as the R-R interval (Figure 7-1). This is the same as the interval between two successive heartbeats. The standard deviation of all the R-R intervals (SDNN, where NN refers to the R-R interval for normal R waves, i.e., those without arrhythmia / artefact), is the commonest linear measure of heart rate variability in the literature. Higher values suggest increased variability.

Figure 7-1 Illustration of an ECG trace and the R-R interval.



As this is a standard deviation measurement, it is influenced by the recording length. A short HR time series of 5-minutes will not incorporate the impact of thermoregulation and the circadian rhythm, while a 24-hour HR time series should. While SDNN is a global measure of HR variability with varying contributions of the PNS, SNS and other regulatory factors, the duration of the time series should always be considered when comparing data. (231) Analysis of 24-hour Holter recordings have suggested patients with SDNN values below 100ms, and therefore decreased variability, have compromised health and an increased cardiovascular burden. (231) Umetani et al (1998) characterised normal SDNN values in different ages ranges following 24-Holter recordings. They found that SDNN decreased with increasing age and patients aged 60-69 had an SDNN 121 ± 32ms; compared to 153 ± 44ms for the 20–29-year category. (313)

Monfredi et al showed that heart rate variability has an inverse non-linear relationship with HR (i.e., increasing HR results in reduced variability), and therefore ideally the SDNN should be corrected for the mean HR to reduce bias and improve reliability. This value (cSDNN) can be calculated by the equation below: (230)

$$\mathrm{cSDNN} = \frac{\mathrm{SDNN}}{e^{-\frac{HR}{58.8}}}$$

It is useful to note that this sort of correction does not exist for other physiological measures such as respiratory rate.

7.1.2 Non-linear analysis measures

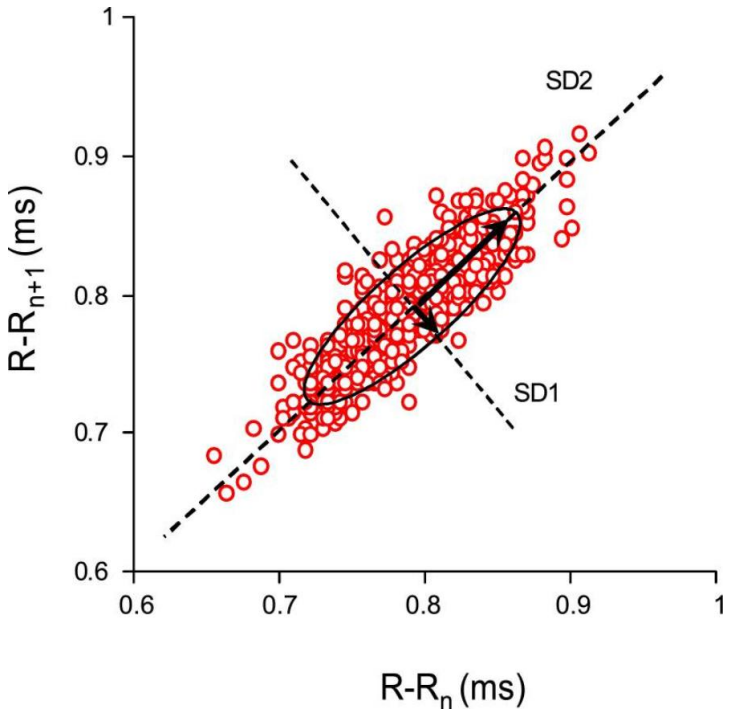
Non-linear measurements allow quantification of the unpredictability of time-series data. This means the relationship cannot be plotted on a straight line and is based on the perspective that physiological time-series, like HR, operate between periods of randomness and periodicity. Some examples of these measures are described below.

7.1.3 Poincare Plots

A Poincare plot is a graphical representation (scatter graph) of the correlation between two consecutive data points in a time-series. For example, between two consecutive R-R intervals (R-R_n and R-R_{n+1}). This is illustrated in Figure 7-2. An ellipse is subsequently fitted to the line of identity (the line where the x-value and y-values are equal). Two values are then calculated from this plot. SD1 is the standard deviation of the points perpendicular to the line of identify and SD2 is the standard deviation along the line of identify. SD1 represents shorter term fluctuations (beat-to-beat), while SD2 represents longer term fluctuations in the time series. (259, 314) SD1 is therefore largely a measure of PNS activity whereas SD2 incorporates both SNS and PNS activity. (315)

Figure 7-2 Poincare plot example

(reproduced with permission from Mani et al (2009)) (259)



7.1.4 Sample entropy

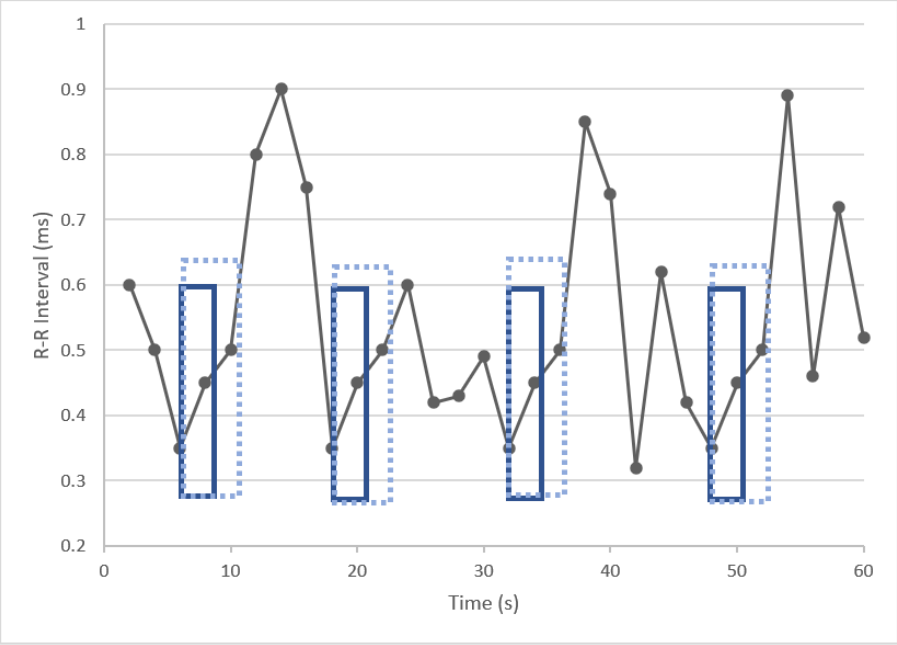
The Oxford English dictionary defines entropy as ‘a state of or tendency toward disorder’. (316) It is therefore simply a mathematical measure of uncertainty or irregularity of a time-series. The idea stems from information theory, which provided a way of determining information contained in a message, first developed by Shannon in the mid-20th century. The index quantifies the number of times a particular signal pattern is repeated and thus measures the complexity of a time-series. (247, 317, 318) It is worth noting that variability and complexity are different measures. For example a sine wave is variable, but not complex. (319) While there are several different entropy measures, sample entropy (SE) was developed by Richard and Moorman and is

independent of the length of the time-series and demonstrates good consistency compared to other measures. (320)

SE measures the probability that sequences of a certain length (*m*) in a time-series are repeated at a later point, with a certain degree of tolerance (*r*). Tolerance (*r*) is akin to a confidence interval. Additionally, it measures whether this pattern of sequences of length *m*, remain similar when the next sample (*m*+1) is included in the sequence. This is illustrated in Figure 7-3. Putting it simply SE quantifies the degree of irregularity vs. regularity in a time series. (247, 321, 322) Low values of SE suggest a greater degree of regularity and less complexity compared to higher values. SE, as a measure of complexity, will account for the interference from multiple regulatory systems affecting a time-series. (270, 319, 323) SE usually has no units ascribed to it. Patients with cardiovascular disease have been found in multiple studies to have a decreased SE of HR, meaning a decreased complexity of the HR signal and decreased ability of the HR to adapt to different stimuli, resulting in a decreased ability to respond to stressors and a higher morbidity during periods of illness. (324) SE of HR also decreases with age and is affected by both gender and obesity. (325-327)

Figure 7-3 Schematic illustration of computing sample entropy.

[adapted from (321, 328)]



B = number of matches of length *m*

A = number of matches of length *m+1*

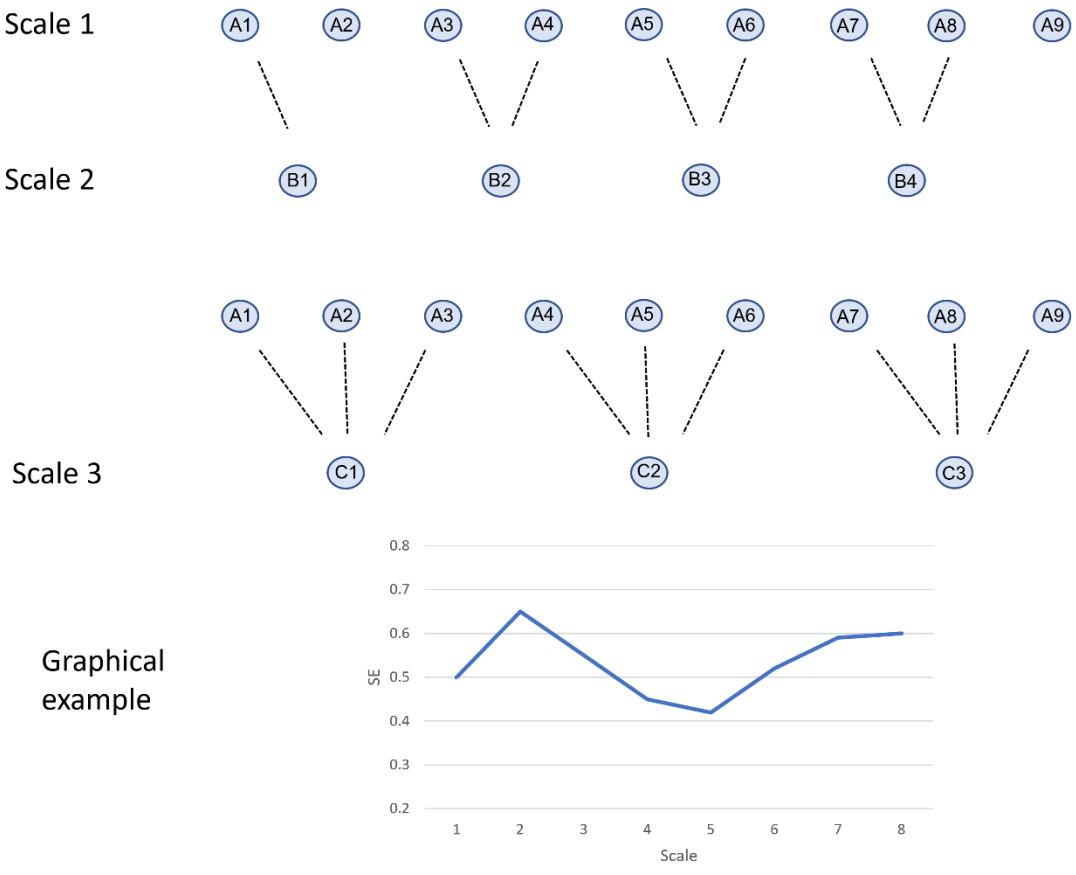
$$SampEn = -\log((\sum A)/(\sum B))$$

7.1.5 Multiscale entropy (MSE)

Multiscale entropy (MSE) is a technique to further define the richness / complexity of a time-series by taking into account the multiple time scales that exist in physiological systems. It is an extension of sample entropy and relies on calculating sample entropy over a range of different scales. By coarse-graining or zooming out of a time series, MSE analysis allows us to assess complexity at varying timescales. Mathematically, this is achieved by creating

several sub-time series from the main time-series and calculating the sample entropy at each scale. This is illustrated in Figure 7-4. This is then plotted to assess cross-scale correlations (with scale on the x-axis and sample entropy on the y axis). A constant MSE graph, where the sample entropy values are roughly the same at each scale or where the values increase, represents a complex time-series. If the values decrease as the scale increases that suggests the time-series lacks structural richness. (329, 330) (247)

Figure 7-4 Multiscale entropy analysis.
(Adapted from (329))



7.1.5 Detrended fluctuation analysis

To understand detrended fluctuation analysis, the following definitions are important to understand first.

Fractal Dimension (289, 331) :

To understand what a dimension is, it is necessary to understand why a straight line is one dimensional, a square two dimensional and cube three. All these objects are self-similar. If you break a line segment into two self-similar pieces, each with the same length, the scale or magnification factor is 2. If you break a square into 4 self-similar pieces, the scale here is 2. Similarly, if you break the square into 9 pieces the scale is 3. So, the square can be broken down into N^2 self-similar copies which are magnified / have a scale of N and in this case a dimension of 2 (i.e., 2-dimension). This idea is shown in Figure 7-5.

Figure 7-5 Understanding the concept of dimension.

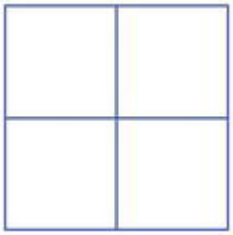
(Adapted from (289, 331)

$2 = 2^1$

Straight line broken into 2 pieces at a scale of 2

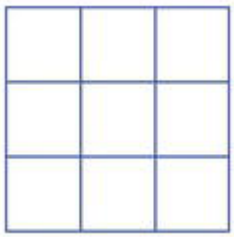
$3 = 3^1$

Straight line broken into 3 pieces at a scale of 3



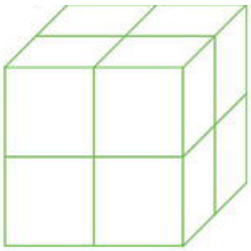
$4 = 2^2$

Square broken into 4 pieces at a scale of 2



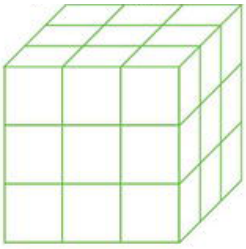
$9 = 3^2$

Square broken into 9 pieces at a scale of 3



$8 = 2^3$

Cube broken into 8 pieces at a scale of 2



$27 = 3^3$

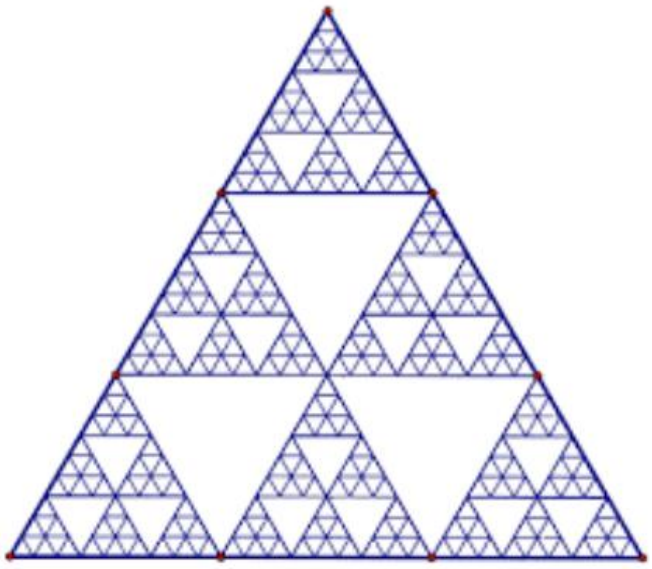
Cube broken into 27 pieces at a scale of 3

Therefore, dimension is the exponent of the number of self-similar pieces with the magnification factor / scale and can be represented by the following equation:

$$\text{How many 'pieces'} = \text{Scale}^{\text{Dimension}}$$

However, what if you had a self-similar structure, that was more complicated? A good example would be the Sierpinski triangle. (Figure 7-6)

Figure 7-6 Sierpinski Triangle



In order to find it's dimension we need to rearrange the above formula into a logarithmic one:

$$Dimension = \frac{\log(number\ of\ self\_similar\ pieces)}{\log(scale)}$$

In the above example the dimension would be fractional.

This number in complicated self-similar structures is termed a fractal dimension. Therefore, fractal dimensions are measures of how ‘complicated’ self-similar structures are.

Fractal time series

The fractal dimensions described above, generally represent geometrical shapes and structures. However, time-series that display self-similarity or self-affinity can have fractal properties. They may exhibit fractal scaling properties in either a statistical sense or an exact sense and can be quantified using fractal dimensions. (289)

Self-Affinity

This is a property of a fractal time series. This differs from self-similarity (seen in purely mathematical or geometrical fractals described above). Self-affinity describes anisotropic scaling whereby the statistical properties of the fractal scale differ along different dimensions. (332)

Power-law function

This is a functional relationship between two quantities whereby a relative change in one lead to a relative change in another. For example, an area of a square is related to the length of its side. If the length is doubled the area is multiplied by four. When the log of the relationships are plotted the result is a straight line.

Scale-free time series

There is no typical distribution of a particular time-series. A scale-free time series will be made up of several sine waves with amplitudes inversely proportional to their frequency. When plotted on a double logarithmic axis, the result will be a straight line. (332)

Non-stationary time-series

This is a time-series where the statistical properties change over time. This time series will often have a trend.

Detrended Fluctuation Analysis

Many physiological time-series have no characteristic length scale, exhibit long-range power-law correlations, are self-affine and are non-stationary. This non-stationary element of physiological time-series is important as it suggests a complexity associated with different trends in the signal or different segments with different statistical properties. DFA accurately quantifies long-range power law correlations of a non-stationary time series, providing a quantitative parameter, known as the scaling exponent (α) which is akin to the fractal dimension. (234, 289)

While the mathematics is complicated, DFA looks at the time-series at various scales, de-trends the data, by subtracting the local trend at each scale, and then calculates the fluctuation at each scale. The fluctuation is akin to the standard deviation. This computation is repeated several times and at different scales to provide a relationship between the fluctuation and the scale. This is

plotted in a double logarithmic axis and the exponent of the straight line is α. The values of α have various meanings: (234)

- α = 0.5 indicates white noise and completely random fluctuation
- 0.5 > α < 1.0 indicates positive autocorrelation, whereby, using heart rate, as an example one large inter-beat interval is followed by another large inter-beat interval.
- α < 0.5 indicates anti-correlation, whereby for example one large inter-beat interval is followed by a short inter-beat interval
- α = 1.5 indicates brown noise
- α = 1.0 indicates 1/f noise or pink noise which can be seen to be between the complete unpredictability of white noise to the very smooth and predictable Brownian noise.

It is important to note, that in physiological time-series the scaling component is not always constant (independent of scale) and therefore crossovers often exist. This means the scaling component (α) differs for different ranges of scales. This is usually due to a change in the correlation properties of the signal at different time scales. (290)

7.2 Appendix 2: Systematic review database search strings

7.2.1 Ovid MEDLINE / EMBASE Search Strategy

Search Strategy - Ovid MEDLINE(R) ALL <1946 to April 12, 2023>

#	Searches
1	exp Lung Diseases, Obstructive/
2	(chronic adj2 (air* adj2 obstruct*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	((lung* or pulmon* or respirat* or bronchopulmon*) adj3 obstruct*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	(COAD or COBD or COPD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5	((centriacinar* or centrilobular* or focal or panacinar* or panlobular* or pulmonar*) adj2 emphysem*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	exp Bronchitis/
7	bronchit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8	Exp Emphysema/

9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp wearable electronic devices/ or exp fitness trackers/ or exp hearing aids/ or exp smart glasses/
11	((fit or fitness) adj3 tracker*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12	fitbit.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13	((wear* or portabl* or home) adj3 activity*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14	(activity* adj3 monitor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15	pedometer*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16	((apple or smart) adj3 watch*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17	((apple* or smart*) adj3 (telephone* or mobile* or cell*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading

	word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18	exp Biosensing Techniques/
19	10 and 18
20	(wear* adj3 (ECG or electrocardiogram)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
21	(wear* adj3 ("blood pressure*" or hyperten*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22	(acceleromet*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
23	((wear* or portabl* or home) adj10 (biosens* or sensor* or track*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
24	(Wear* adj3 monitor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25	((wear* or portabl* or home*) adj3 technolog*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol

	supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26	((wear* or portabl* or home*) adj3 (garment* or cloth* or shirt* or t?shirt* or blouse* or vest* or underwear)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
27	exp Textiles/
28	exp oximetry/ or exp blood gas monitoring, transcutaneous/
29	oximetr*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
30	((wear* or portabl* or home*) adj3 patch*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
31	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	9 and 31
33	Limit 32 to (English language)

Note: For the EMBASE search an additional line limiting 33 to (article or article in press) was used.

7.2.2 CINAHL Search Strategy

#	Query	Limiters/Expanders	Last Run Via
S34	S9 AND S33	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S33	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S32	((wear* or portabl* or home*) N3 patch)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S31	oximetr*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S30	(MM "Oximetry+") OR (MM "Pulse Oximetry") OR (MM "Blood Gas Monitoring, Transcutaneous") OR (MM "Oximeters+") OR (MH "Pulse Oximeters")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S29	(MM "Textiles")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S28	((wear* or portabl* or home*) N3 (garment* or	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases

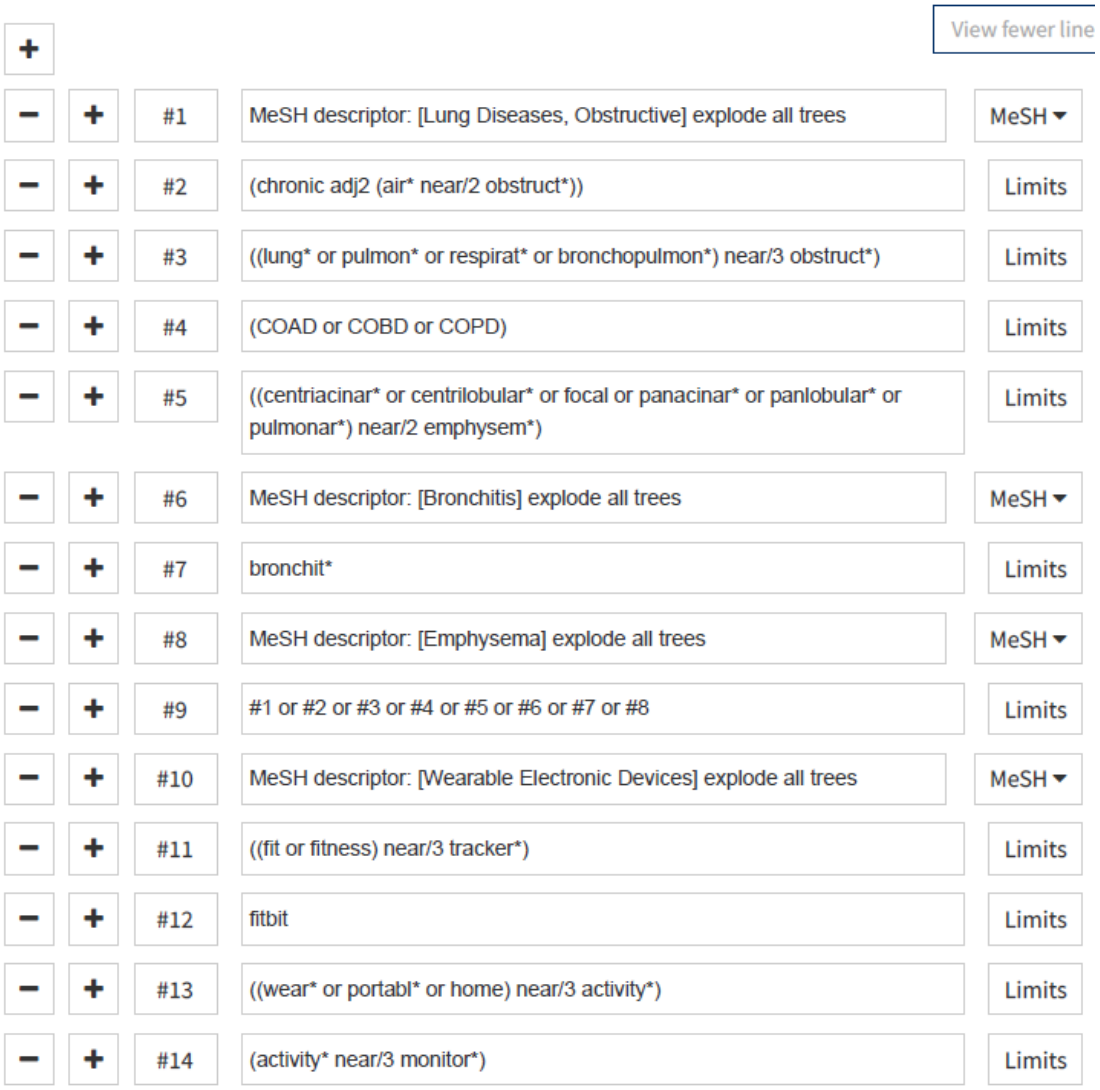
	t-shirt*))	Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL Plus
S27	((wear* or portabl* or home*) N3 technolog*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S26	(Wear* N3 monitor*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S25	((wear* or portabl* or home) N10 (biosens* or sensor* or track*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S24	(acceleromet*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S23	(wear* N3 ("blood pressure*" or hyperten*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S22	(wear* N3 (ECG or electrocardiogram))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S21	(MM "Biosensing Techniques+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S20	((apple* or smart*) N3 (telephone* or mobile* or cell*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus

S19	((apple or smart) adj3 watch*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S18	pedometer*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S17	(activity* N3 monitor*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S16	((wear* or portabl* or home) N3 activity*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S15	fitbit	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S14	((fit or fitness) N3 tracker*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S13	(MM "Smart Glasses")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S12	(MM "Hearing Aids+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S11	(MM "Fitness Trackers")	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases

		Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL Plus
S10	wearable electronic devices	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S8	(MM "Emphysema+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S7	bronchit*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S6	(MM "Bronchitis+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S5	((centriacinar* or centrilobular* or focal or panacinar* or panlobular* or pulmonar*) N2 emphysem*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S4	(COAD or COBD or COPD)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S3	((lung* or pulmon* or respirat* or bronchopulmon*) N3 obstruct*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus

S2	(chronic N2 (air* N2 obstruct*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus
S1	(MM "Lung Diseases, Obstructive+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus

7.2.3 CENTRAL Database Search Strategy



−	+	#15	pedometer*	Limits
−	+	#16	((apple or smart) near/3 watch*)	Limits
−	+	#17	((apple* or smart*) near/3 (telephone* or mobile* or cell*))	Limits
−	+	#18	MeSH descriptor: [Biosensing Techniques] explode all trees	MeSH ▾
−	+	#19	(wear* near/3 (ECG or electrocardiogram))	Limits
−	+	#20	(wear* near/3 ("blood pressure*" or hyperten*))	Limits
−	+	#21	acceleromet*	Limits
−	+	#22	((wear* or portabl* or home) near/10 (biosens* or sensor* or track*))	Limits
−	+	#23	(Wear* near/3 monitor*)	Limits
−	+	#24	((wear* or portabl* or home*) near/3 technolog*)	Limits
−	+	#25	((wear* or portabl* or home*) near/3 (garment* or t-shirt*))	Limits
−	+	#26	MeSH descriptor: [Textiles] explode all trees	MeSH ▾
−	+	#27	MeSH descriptor: [Oximetry] explode all trees	MeSH ▾
−	+	#28	oxiemtr*	Limits
−	+	#29	((wear* or portabl* or home*) near/3 patch*)	Limits
−	+	#30	MeSH descriptor: [Fitness Trackers] explode all trees	MeSH ▾
−	+	#31	MeSH descriptor: [Hearing Aids] explode all trees	MeSH ▾
−	+	#32	MeSH descriptor: [Smart Glasses] explode all trees	MeSH ▾
−	+	#33	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or	Limits
−	+	#34	#9 and #33	Limits

7.2.4 IEEE Search Terms used

1. obstructive lung disease
2. (All Metadata:COPD) OR (All Metadata:COAD) OR (All Metadata:COBD)
3. bronchitis
4. emphysem*
5. (All Metadata:wear* electronic) OR (All Metadata:wear* computer) OR (All Metadata:smart watch)
6. (All Metadata:fitness tracker) OR (All Metadata:fitbit) OR (All Metadata:pedometer)
7. (All Metadata:activity monitor) OR (All Metadata:accelerometer) OR (All Metadata:wear* sensor)
8. ((((obstructive lung disease)) OR ((All Metadata:COPD) OR (All Metadata:COAD) OR (All Metadata:COBD))) OR (bronchitis)) OR (emphysem*)
9. (All Metadata:textiles) OR (All Metadata:oximetr*) OR (All Metadata:wearable patch) OR (All Metadata:wearable garment) OR (All Metadata:wearable blood pressure) OR (All Metadata:wearable electrocardiogram)
10. (All Metadata:wear* technolog*)
11. (All Metadata:fitness tracker) OR (All Metadata:hearing aids) OR (All Metadata:smart glasses)
12. (((((((All Metadata:wear* electronic) OR (All Metadata:wear* computer) OR (All Metadata:smart watch))) OR ((All Metadata:fitness tracker) OR (All Metadata:fitbit) OR (All Metadata:pedometer))) OR ((All Metadata:activity monitor) OR (All Metadata:accelerometer) OR (All Metadata:wear* sensor))) OR ((All Metadata:textiles) OR (All Metadata:oximetr*) OR (All Metadata:wearable patch) OR (All Metadata:wearable garment) OR (All Metadata:wearable blood pressure) OR (All Metadata:wearable electrocardiogram))) OR ((All Metadata:wear* technolog*))) OR ((All Metadata:fitness tracker) OR (All Metadata:hearing aids) OR (All Metadata:smart glasses))
13. ((((((((((((No Keywords Specified))) AND ((All Metadata:wear* electronic) OR (All Metadata:wear* computer) OR (All Metadata:smart watch))) OR ((All Metadata:fitness tracker) OR (All Metadata:fitbit) OR (All Metadata:pedometer))) OR ((All Metadata:activity monitor) OR (All Metadata:accelerometer) OR (All Metadata:wear* sensor))) OR ((All Metadata:textiles) OR (All Metadata:oximetr*) OR (All Metadata:wearable patch) OR (All Metadata:wearable garment) OR (All Metadata:wearable blood pressure) OR (All Metadata:wearable electrocardiogram))) OR ((All Metadata:wear* technolog*))) OR ((All Metadata:fitness tracker) OR (All Metadata:hearing aids) OR (All Metadata:smart glasses))) AND ((No Keywords Specified))) AND (obstructive lung disease)) OR ((All Metadata:COPD) OR (All Metadata:COAD) OR (All Metadata:COBD))) OR (bronchitis)) OR (emphysem*)

7.3 Appendix 3: list of excluded studies with rationale

Inaccurate COPD diagnosis

Bender BG, Depew A, Emmett A, et al. A Patient-Centered Walking Program for COPD. *Chronic Obstr Pulm Dis* 2016; **3**(4): 769-77.

Lin WY, Verma VK, Lee MY, Lin HC, Lai CS. Prediction of 30-Day Readmission for COPD Patients Using Accelerometer-Based Activity Monitoring. *Sensors (Basel)* 2019; **20**(1).

Martinez CH, Moy ML, Nguyen HQ, et al. Taking Healthy Steps: rationale, design and baseline characteristics of a randomized trial of a pedometer-based Internet-mediated walking program in veterans with chronic obstructive pulmonary disease. *BMC Pulm Med* 2014; **14**: 12.

Moy ML, Collins RJ, Martinez CH, et al. An Internet-Mediated Pedometer-Based Program Improves Health-Related Quality-of-Life Domains and Daily Step Counts in COPD: A Randomized Controlled Trial. *Chest* 2015; **148**(1): 128-37.

Moy ML, Martinez CH, Kadri R, et al. Long-Term Effects of an Internet-Mediated Pedometer-Based Walking Program for Chronic Obstructive Pulmonary Disease: Randomized Controlled Trial. *J Med Internet Res* 2016; **18**(8): e215.

Orme MW, Weedon AE, Saukko PM, et al. Findings of the Chronic Obstructive Pulmonary Disease-Sitting and Exacerbations Trial (COPD-SEAT) in Reducing Sedentary Time Using Wearable and Mobile Technologies With Educational Support: Randomized Controlled Feasibility Trial. *JMIR Mhealth Uhealth* 2018; **6**(4): e84.

Riis HC, Jensen MH, Cichosz SL, Hejlesen OK. Prediction of exacerbation onset in chronic obstructive pulmonary disease patients. *J Med Eng Technol* 2016; **40**(1): 1-7.

Tabak M, Vollenbroek-Hutten MM, van der Valk PD, van der Palen J, Hermens HJ. A telerehabilitation intervention for patients with Chronic Obstructive Pulmonary Disease: a randomized controlled pilot trial. *Clin Rehabil* 2014; **28**(6): 582-91.

Wu R, Liaqat D, de Lara E, et al. Feasibility of Using a Smartwatch to Intensively Monitor Patients With Chronic Obstructive Pulmonary Disease: Prospective Cohort Study. *JMIR Mhealth Uhealth* 2018; **6**(6): e10046.

Conference Proceedings

PEDOMETER AS A TOOL FOR QUALITY OF LIFE IMPROVEMENT IN COPD PATIENTS. *Respirology* 2018; **23**(S2): 244-5.

Armstrong M, Hume E, McNeillie L, et al. P241 A pilot RCT assessing the inclusion of physical activity counselling to standard care pulmonary rehabilitation in patients with COPD. *Thorax* 2021; **76**(Suppl 1): A219-A.

Cao D, Zhang Z, Liang H, et al. Application of a Wearable Physiological Monitoring System in Pulmonary Respiratory Rehabilitation Research. 2018 11th International Congress on Image and Signal Processing, BioMedical Engineering and Informatics (CISP-BMEI); 2018 13-15 Oct. 2018; 2018. p. 1-6.

Collins R, Martinez CH, Kadri R, et al. An Internet-Mediated, Pedometer-Based Walking Program Improves HRQL In Veterans With COPD. B96 HIGHLIGHTS IN PULMONARY REHABILITATION: 2013: A3642-A.

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7.4 The acceptability of wearable technology for long-term respiratory disease: a cross-sectional survey

The acceptability of wearable technology for long-term respiratory disease: a cross-sectional survey

You are being invited to participate in a research study titled: **the acceptability of wearable technology for long-term respiratory disease: a cross-sectional survey.** This study is being done by Dr Amar Shah and Dr Swapna Mandal who are respiratory doctors at the Royal Free Hospital in Hampstead, London and will form part of Dr Amar Shah's PhD thesis being done at University College London.

What is the purpose of this survey?
The purpose of this research study is to try and find out whether wearable technology would be acceptable to patients who suffer with long-term respiratory disease, for example COPD, asthma, lung fibrosis, lung cancer, bronchiectasis etc.

What is wearable technology?
Wearable technology is any electronic device that is worn by someone close to and/or on the surface of the skin. It can collect information about that person for example, body signals such as heart rate or breathing rate or oxygen levels, activity levels, sleep patterns etc. It can track these signals, monitor progress, and let that person know how the signals have changed (feedback). Most of the wearable technology that is available to buy has not been tested in a research study and the results can sometimes be inaccurate. Examples of wearable technology can be seen in the picture below:

We are interested in getting patients' views on the following:

1) Is new wearable technology something they would be interested in trying in the future?
2) Do they think new wearable technology could help them with their lung conditions?
3) What features are important in any new technology?

What will the information be used for?
The information from this survey will be used to hopefully guide future development of new technology that is specific to patients with respiratory disease. It will also give us an idea on what features are important to patients when designing new technology. We will aim to publish the information in a medical journal. Your answers are completely anonymous and you will not be identifiable from the information.

How will the information be processed and stored?
All the information on this survey is treated confidentially by SurveyMonkey. All data is collected and the content is stored in a manner consistent with industry security standards in accordance with the Data Protection Act 2018 and is General Data Protection Regulation (GDPR) compliant. All the information we collect about you during the course of the research will be kept strictly confidential and only the research team directly involved in the study will have access to the answers. You will not be able to be identified in any publications or reports from this research. We will share the anonymised data with selected non-commercial third parties, such as respiratory charities.

We believe there are no known risks associated with this research study. However, as with

any online related activity the risk of a breach is always possible.

Your participation in this study is entirely voluntary and will take approximately 10-15 minutes (including reading the information sheet) to complete. You do not have to answer any questions you do not want to. If you are happy to take part you will be asked to fill a consent form.

For further information about the study please download the participant information sheet:
[https://drive.google.com/file/d/1kTz_Zn3lYXziqNMrmoJdHUEN3kvXIE_G/view?usp=sharing] and retain this for your records.

1. I have read the above information and the patient information sheet. Please tick one of the following options:

☐ I wish to proceed with this study and am happy to give my consent

☐ I do not wish to proceed with this study

2. Which of the following lung conditions are you currently affected by? If not listed please use the other box and write the condition down. (Please tick all that apply).

☐ Chronic obstructive lung disease (COPD)

☐ Obstructive sleep apnoea (OSA)

☐ Asthma

☐ Lung cancer

☐ Interstitial lung disease (ILD), including idiopathic pulmonary fibrosis (IPF) and sarcoidosis

☐ Bronchiectasis

☐ Long COVID

☐ Other ……..

3. Do you currently wear something to monitor your health and wellbeing?

☐ Yes (Go to Q4) ☐ No (Go to Q8, page 5)

4. What type of device to you currently wear to monitor your health and wellbeing? Please choose the type of device from the following list. If not listed please use the 'other' box and write down the name of the device. (Please tick all that apply).

☐ Smart watch (e.g., Apple watch, Samsung watch, Garmin watch or others that are designed to monitor your health and well-being)

☐ Fitbit®

☐ Smart glasses that are designed to monitor your health and wellbeing

☐ Smart Ring (e.g., oura rings or others that monitor your health and wellbeing)

☐ Pedometer or step counter

☐ Clothing (including T-shirt, vest etc./ that monitor your health and wellbeing with sensors)

☐ Patch (e.g., glucose monitoring patch, or others that monitor your health and wellbeing)

☐ Belts (e.g., across your chest or tummy or elsewhere that are able to monitor your health and wellbeing)

☐ Other (please specify)
……

5. What do you use this wearable technology for, specifically in relation to your lung condition? (Tick all that apply)

☐ To monitor symptoms of my lung condition through measurements, such as breathing rate, respiratory effort, oxygen levels etc.

☐ To remind me to take medication for my lung condition

☐ To encourage exercise or other self-care for my lung condition

☐ To help predict when I might become unwell from my lung condition

☐ Not applicable

☐ Other (please specify)

……..

6. What do you use this wearable technology for, in relation to your general health? (Tick all that apply)

☐ General health measurements e.g., heart rate, sleep quality, oxygen levels

☐ To track my progress against general health goals

☐ To remind me to take medication

☐ To encourage exercise or other self-care

☐ Not applicable Other (please state)

☐ Other (please specify)

……

7. I find the device I use to monitor my health useful.

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

8. I would like to learn about new technology that I can wear.

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

9. Wearable technology will increase my confidence to monitor my long-term lung condition at home.

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

10. I believe that wearable technology will reduce the number of times I see a doctor or my community, in relation to my lung condition.

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

11. Wearable technology that helps me with the following would be useful for me. (Tick all that apply)

☐ Detects when I am becoming unwell

☐ Helps me to manage my symptoms (e.g. breathlessness, cough, chest tightness etc.)

☐ Reminds me to take my medication

☐ Encourages me to exercise and become more active

☐ Improves my sleep quality

☐ Other (please specify)

……..

12. I think that the wearable technology that is currently available is accurate.

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

13. Which of the following 3 characteristics of wearable technology are most important to you?

☐ Easy to learn

☐ Easy to use

☐ Battery life

☐ Price and brand

☐ Look and feel (aesthetics)

☐ Accurate (correct) results

☐ Privacy of data collected

☐ Other (please specify)
……

14. How would you prefer to access the information recorded / monitored from the wearable technology (Tick all that apply)

☐ Own mobile phone

☐ Through the wearable technology itself (e.g., screen directly on technology)

☐ A computer or tablet

☐ An extra monitor that attaches to the wearable device

☐ I would not want to access any of the information and would prefer it to go directly to my healthcare provider (e.g., doctor, nurse, physiotherapist)

☐ Other (please specify)
……..

15. It is important that the wearable technology links to other devices that I use to monitor my health (e.g., peak flow meter, exercise diary, symptom diary).

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

16. It is important that the wearable technology has undergone testing in an appropriate clinical trial and has been approved by regulatory bodies.

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

17. The wearable technology should look the same as other everyday items so that other people don't know I am wearing it.

Strongly agree	Agree	Somewhat Agree	Neutral	Somewhat Disagree	Disagree	Strongly Disagree
☐	☐	☐	☐	☐	☐	☐

18. I think wearable technology will become a normal part of everyday life in the future.

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

19. I am more likely to use wearable technology if I have the support from my friends and family

Strongly disagree	Disagree	Somewhat disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
☐	☐	☐	☐	☐	☐	☐

20. Do you have any other comments or thought on wearable technology to manage your lung condition?

Demographic data

The next part of the survey is to give us a bit of information about you. This information is completely anonymous but feel free to end the survey if you do not wish to answer this section.

21. Please select what age range you fit into.

☐ 18 – 21 years
☐ 22 – 30 years
☐ 31 – 40 years
☐ 41 – 50 years
☐ 51 – 60 years
☐ 61 – 70 years
☐ 71 – 80 years
☐ 81 – 90 years
☐ Above 90 years

22. What is your gender?

☐ Male
☐ Female
☐ Non-binary
☐ Intersex
☐ Transgender
☐ Other ……..
☐ Prefer not to say

23. What is your ethnicity?

☐ Asian Other
☐ Bangladeshi
☐ Black African
☐ Black British
☐ Black Caribbean
☐ Chinese
☐ Hispanic or Latino
☐ Indian
☐ Pakistani
☐ White British
☐ Mixed
☐ Other (please specify)

24. Which of the following best describes your approximate household income last year?

☐ £0
☐ Between £1 and £9,999
☐ Between £10,000 and £24,999
☐ Between £25,000 and £49,999
☐ Between £50,000 and £74,999
☐ Between £75,000 and £99,999
☐ Over £100,000
☐ Prefer not to answer

7.5 Matlab code used for the thesis

The code used for this thesis has been uploaded as part of a Github repository and can be freely viewed from the following link:

https://github.com/amarshah191288/PhD-Thesis.git

The repository is publicly available and archived. To see the code, please access the individual branches labelled:

- Stable-COPD
- Exacerbating-COPD
- Health-controls

These can be accessed on the main page by switching from the ‘main’ branch.

7.6 Overnight limited cardio-respiratory polygraphy

Cardiorespiratory polygraphy is a non-invasive multi-channel overnight sleep study which records several parameters including:

- Nasal flow (and as a result respiratory rate)
- Oxygen saturations
- Heart rate
- Abdominal and thoracic movements (through piezoelectric bands)

Prior studies have shown that this type of sleep study has a high sensitivity and specificity for the diagnosis of sleep disordered breathing compared to a full polysomnography (which includes electroencephalography amongst other signals), with one study showing the area under the ROC curve for AHI ≥5, ≥10 and ≥15 was 0.896, 0.907 and 0.862 respectively. (333) Subsequent studies and guidelines now accept these studies as gold standard diagnostic tools for sleep disordered breathing. (52, 334)

The signals from this study are manually scored with previously identified American Association of Sleep Medicine criteria (52) to define a hypopnoea and apnoea as follows:

- Hypopnoea: ≥ 30% reduction in nasal flow which is followed by a 3% or 4% desaturation.
- Apnoea: ≥ 90% reduction in nasal flow which may or may not be followed by a desaturation

The abdominal and thoracic belt movement is then used to characterise the apnoeas and hypopnoeas as either obstructive (ongoing abdominal / thoracic belt movement), central (no movement at all in these belts) or mixed.

This leads to an overall apnoea/hypopnoea index (AHI) and categorises these into obstructive, central and/or mixed events to give an overall diagnosis.

The device used for this study (Embletta MPR PG ambulatory (unattended) polygraph sleep monitor (Stowood scientific instruments ltd)) is routinely used at the Royal Free Hospital sleep service.

7.7 Measures of health-related quality of life

A variety of different health-related quality of life scores and measures were used throughout all the studies. The CAT score and MRC score have already been described in the introduction (1.1.5) and so have not been repeated here.

7.7.1 Epworth sleepiness scale

The Epworth sleepiness scale (ESS) was first developed by Dr Johns in 1990, named after the Epworth hospital in Melbourne. It is a validated eight item questionnaire which is used to indicate daytime somnolence which is a prominent symptom in patients with sleep disordered breathing. Johns showed that it can differentiate between simple snorers, those with OSA and healthy controls. In patients with OSA the ESS is also significantly correlated to the respiratory disturbance index and the minimum oxygen saturation recorded. (335, 336) However, the correlation between AHI and ESS has been poor, with two studies finding no association between the two (R^2 0.011), (337) and (R^2 = 0.001). (338)

The ESS asks patients to rate between 0 – 3 (0 = no chance of dozing, 1 = slight chance, 2 = moderate chance, 3 = high chance) how likely they are to fall asleep in the following scenarios:

- 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 if allowed to do so
- Sitting and talking to someone
- Sitting quietly after lunch without alcohol
- In car or bus stopped for a few minutes

A score of > 10 suggests mildly increased daytime sleepiness, with a score ≥ 16 suggestive of excessive daytime somnolence. (335) There are several limitations to the ESS. Several studies have failed to demonstrate an association between ESS and OSA severity. Furthermore, only about 40% of patients with moderate-severe OSA will have an ESS greater than the cut-off of 10, and importantly some individuals with low ESS scores will give positive responses to different questions regarding sleepiness. (339)

7.7.2 Sleep questionnaire

This baseline sleep questionnaire was developed specifically for this study. The questionnaire aimed to encapsulate a concise sleep history, to understand participant symptomatology. The first part of the questionnaire asked participants to rate between 0 – 3 (0 = never, 1 = occasionally / some

days, 2 = frequently / most days, 3 = always / every day) how likely they are to suffer with the following symptoms:

- Snoring while sleeping at night.
- Choking episodes or waking up gasping for breath.
- Someone has seen them stop breathing in their sleep.
- Breathless when lying flat at night.
- Early morning headaches.
- Increased daytime sleepiness.
- Confusion in the morning.
- Waking up un-refreshed.

Participants were then asked a series of questions including:

- Whether they wake up overnight to pass urine?
- How many hours they sleep at night?
- Whether they have trouble getting to sleep at night.
- The average time it takes them to fall asleep?
- How long they take to get back to sleep if woken in the middle of the night?
- Do they currently drive?
- If they do drive, they were asked about whether they had had any of the following since starting CPAP:
    - A road traffic accident because of falling asleep
    - Head nodding or bobbing

- Hitting the rumble strip on the motor way
- Regular use of alerting manoeuvres such as keeping the windows open, stopping to stretch, or listening to loud music to help stay awake.

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