PHYSICAL ACTIVITY IN FIBROTIC INTERSTITIAL LUNG DISEASE

by

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B.Sc., The University of British Columbia, 2016

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate and Postdoctoral Studies
(Experimental Medicine)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

March 2018

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Abstract

Fibrotic interstitial lung diseases (ILDs) are characterized by inflammation and fibrosis of the pulmonary parenchyma. In addition to the primary symptoms of dyspnea and cough, many patients with fibrotic ILD experience extrapulmonary deficits that can interfere with their ability to stay active. This is a concern as the maintenance of physical activity plays an important part in independence and prevention of deconditioning in patients with fibrotic ILD. However, the impact of common extrapulmonary deficits on daily physical activity of these patients is not known.

Accordingly, in chapter 2, we examined the impact of depression, anxiety, poor sleep quality, and pain on daily physical activity in a cohort of 111 patients with fibrotic ILD. Extrapulmonary deficits were assessed using the Hospital Anxiety and Depression Scale, the Pittsburgh Sleep Quality Index, and the Brief Pain Inventory short form. Patients' physical activity was monitored for seven consecutive days using waist and wrist tri-axial accelerometers, in addition to the self-reported International Physical Activity Questionnaire long form (IPAQ-LF). Although depression and pain were moderately associated with lower step count on unadjusted analysis, extrapulmonary deficits did not independently predict lower physical activity when adjusting for basic demographics and ILD severity. However, we identified higher pain severity to be an independent predictor of lower step count using a multivariable stepwise approach. This finding suggests that pain may be a potential area that could be targeted by interventions to help patients maintain physical activity.

In chapter 3, we examined the validity of the IPAQ-LF and estimated the minimally important difference (MID) for moderate-to-vigorous physical activity (MVPA) in patients with fibrotic ILD. We found the IPAQ-LF to have acceptable validity based on its measurements having moderate-to-strong correlations with corresponding waist accelerometer data and relevant clinical outcomes. The MID for weekly MVPA was estimated to be less than 60 minutes/week using the anchor-based approach. This indicates that adding only 60 minutes of MVPA per week is a realistic goal that brings meaningful benefits to patients with fibrotic ILD and provides a goal threshold for future clinical trials.

Lay Summary

Fibrotic interstitial lung diseases (ILDs) are a group of chronic illnesses characterized by scarring and inflammation of the lungs. Physical activity in patients with fibrotic ILD is important in maintaining their functional capacity and quality of life; however, symptoms such as depression, anxiety, poor sleep quality, and pain can interfere with patients' ability to stay active. Our study examined how depression, anxiety, poor sleep quality, and pain impact daily physical activity in patients with fibrotic ILD using questionnaires and waist activity monitors to track step count. In addition, we examined what could be considered a meaningful change in moderate-to-vigorous physical activity for patients with fibrotic ILD. We found pain to be a potential area that could be targeted in these patients to improve daily physical activity, and estimate that patients with fibrotic ILD can gain meaningful improvements in their physical activity by exercising an additional 60 minutes/week at moderate-to-vigorous intensity.

Preface

All of the work presented was conducted at the Centre for Heart Lung Innovation at St. Paul's Hospital and at The Lung Centre at Vancouver General Hospital. The project has received ethics and operational approval from the University of British Columbia Providence Health Care Research Ethics Board (H16-02980) and Vancouver Coastal Health Research Institute (V16-02980) under the project title "Predictors of physical activity in fibrotic interstitial lung disease." Chapters 2 and 3 of the thesis are being prepared for submission to peer-reviewed journals; however, at the time of writing, this dissertation is original and unpublished.

The work presented in chapters 2 and 3 was co-conceived and designed by Dr. Chris Ryerson and myself. I was responsible for all major areas of patient recruitment, data collection and analysis, interpretation of the data, and writing of manuscripts. Drs. Chris Ryerson and Nasreen Khalil provided access to their clinic patients. Drs. Pat Camp, Jordan Guenette, and Sabina Guler provided valuable input on study design and data interpretation and were involved throughout the project and manuscript edits for both chapters. Dr. Jeffrey Swigris was also involved in data analysis and interpretation for chapter 3. Dr. Chris Ryerson was the supervisory author on all the work presented in this dissertation and was involved throughout project conception and writing of manuscripts.

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List of Abbreviations

BPI-SF	– Brief Pain Inventory short form
CI	– Confidence interval
COPD	– Chronic obstructive pulmonary disease
DLCO	– Diffusing capacity of the lungs for carbon monoxide
DLW	– Doubly labeled water
EE	– Energy expenditure
EQ-5D	– European Quality of Life 5-Dimensions 5-level version
FEV_1	– Forced expiratory volume in one second
FVC	– Forced vital capacity
HADS	– Hospital Anxiety and Depression Scale
Hz	– Hertz
ILD	– Interstitial lung disease
IPAQ-LF	– International Physical Activity Questionnaire long form
IPF	– Idiopathic pulmonary fibrosis
IQR	– Interquartile range
kg	– Kilogram
LFE	– Low frequency extension
m	– Metre
mins	– Minutes
MET	– Metabolic equivalent of task

MID	– Minimally important difference
MVPA	– Moderate-to-vigorous physical activity
PRO	– Patient-related outcome
PSQI	– Pittsburgh Sleep Quality Index
SD	– Standard deviation
SEM	– Standard error of measurement

Acknowledgements

I would like to first express my gratitude to my supervisor Dr. Chris Ryerson, who has given me the valuable opportunity of managing my own clinical research project. His patience in teaching me clinical research knowledge and soft skills of time management and self-directed learning cannot be thanked enough. He has been an inspiration to work with and a level-minded and supportive mentor throughout my graduate training.

I would like to thank my committee members, Drs. Pat Camp and Jordan Guenette for their support and prompt and timely advice. I would also like to thank Dr. Nasreen Khalil and current and past trainees of Dr. Ryerson's team that have helped with patient recruitment, study design, data collection and analysis, and manuscript edits. I would like to thank the patients who have participated in this study and showed their genuine support and interest in our research.

Lastly, I would like to thank the research and clinic staff at the Pacific Lung Health Centre. I would like to especially extend my gratitude to Fran Schooley, Joey Fu, and Grace Lee who helped me settle in when I was a new graduate student.

Dedication

To my supportive family and friends.

I am thankful for your love and encouragement

throughout all these years.

Chapter 1: Introduction

1.1 General introduction

This dissertation presents two research chapters stemming from a large prospective cohort study that examined daily physical activity of patients with fibrotic interstitial lung disease (ILD). The first chapter explored the association of extrapulmonary comorbidities with physical activity, while the second half of the thesis examined the validity of a commonly used physical activity self-report and proposed a clinically meaningful change in activity levels of patients with fibrotic ILD.

This introduction provides a comprehensive overview on various methods of measuring physical activity, background information on fibrotic ILD, and the importance of comorbidities and physical activity in this patient population. In addition, this chapter discusses the concept of minimally important difference (MID), its significance in clinical and research settings, and ways to calculate MID.

1.2 Definition and methods of measuring physical activity

Physical activity is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure."[1] This definition differs from the term "exercise", which is a subset of physical activity that is planned, structured, and purposeful with the goal of improving or maintaining physical fitness.[1] While the benefits of regular exercise are well-documented in various health conditions, the maintenance of physical activity that occurs outside of exercise is similarly important for prevention of chronic conditions and promotion of better quality of life.[2] This has warranted a need and demand to accurately measure and monitor physical activity by researchers, healthcare providers, and patients. However, physical activity is a complex phenomenon that can be quantified in several ways (*e.g.,* step count, energy expenditure, acceleration, minutes of activity, intensity) using various tools. This section highlights eight major methods of measuring physical activity in a research setting and everyday life, in addition to discussing the strengths and weaknesses of each approach.

1.2.1 Doubly labeled water

The doubly labeled water (DLW) method is considered as the gold standard of measuring total energy expenditure, and is often used to validate other methods of physical activity measurements.[3] The protocol requires patients to ingest a dose of DLW that contains stable oxygen (^{18}O) and hydrogen (^{2}H) isotopes and provide urine samples at specific times over 7-14 days that can be compared to the baseline sample provided prior to DLW ingestion.[4] The isotopes in DLW are eliminated from the body at different rates once they reach equilibrium with total body water: while ^{2}H is excreted via only water, ^{18}O is eliminated via water and carbon dioxide. The rate of carbon dioxide production can be calculated due to this difference in methods and rates of elimination of ^{2}H and ^{18}O. The subject's total and activity energy expenditure can then be derived by applying the rate of carbon dioxide production to specific formulae.

The DLW method is highly accurate and relatively non-invasive for patients, making it easily applicable for use in various populations including infants, pregnant women, and the elderly.[5–7] However, the DLW method is mainly hindered by the high cost of DLW and other equipment and expertise required for analysis. The technique is also limited to providing averaged energy expenditure over the assessment period, and does not provide specific details or qualitative data on physical activity. These limitations can make it difficult to apply the DLW method in large groups involving repeated follow-ups or lengthy periods of measurement.

1.2.2 Calorimetry

Direct calorimetry measures the rate of heat loss in subjects to quantify their metabolic rate.[8] On the other hand, indirect calorimetry measures the volumes of inspired and expired gas and the concentration of oxygen and carbon dioxide to derive energy expenditure.[9] While both types of calorimetry provide highly accurate measurements, they require specific equipment or calorimetric heat chambers, in which patients are confined to the laboratory space. These limitations make the use of calorimetry difficult for studying physical activity in free living conditions. Moreover, calorimetric measurements fail to provide other details of physical activity such as frequency, duration, and intensity.

1.2.3 Self-report questionnaires

The use of self-report questionnaires is one of the most common methods of assessing physical activity.[10] Some of the well-studied, frequently used self-reports include the International Physical Activity Questionnaire,[11] Recent Physical Activity Questionnaire,[12,13] 7-day Physical Activity Recall,[14] and Modifiable Activity Questionnaire.[15] These questionnaires vary in how they quantify physical activity (*e.g.,* time, calories, activity scores), how the data are obtained (*e.g.,* paper and pencil, computer, in-person/phone interview), and the quality of the data obtained (*e.g.,* recent recall, reporting of habitual activities, differentiating leisure and non-leisure activity), providing researchers with the flexibility to address specific questions. While physical activity data from self-report questionnaires can be inconsistent with DLW measurements,[16] these questionnaires can be easily administered by researchers and healthcare providers, are less burdensome for patients, and are more cost effective than other methods. They are also useful for studying physical activity at the group level and gathering details on different categories of activity (*e.g.,* work-related activity, leisure, transportation-related activity, housework-related activity), and are accurate in detecting intense physical activity.[11,13,16,17] However, self-report questionnaires are primarily dependent on patients' memory and face the disadvantages of recall and social desirability biases. Moreover, they are less robust for measuring light or moderate physical activity and energy expenditure.[18–21]

1.2.4 Self-report diaries and logs

Self-report diaries or logs require patients to record their physical activity in real time throughout the day. Researchers or healthcare providers can use standardized logs or design their own self-reports geared towards their needs. While this method can provide detailed data and partially overcome recall errors or biases that are more susceptible in self-report questionnaires,[22] logs and diaries are burdensome for patients and time-consuming for researchers to analyze. These types of self-reports are more prone to participant reactivity, in which the patients change their behaviour due to the awareness of being observed.[23] Moreover, logs and diaries can still be subject to recall errors and memory bias when the forms are not completed in real time.

1.2.5 Direct observation

An independent observer is required to watch and record one's physical activity in direct observation. This method can be useful when subjects have difficulty recalling their physical activity, particularly in children.[24] Direct observation also allows researchers to obtain contextual information and details of physical activity that are otherwise difficult or not possible to collect using other methods. However, this method is not ideal for large cohort or population-based studies as it provides limited objective physical activity data and requires significant time and energy of the researchers. Direct observation is also prone to participant reactivity.[23]

1.2.6 Accelerometers

These devices can be worn on patient's waist, thigh, or wrist throughout the day to record the acceleration of movements in up to three orthogonal planes.[25] The acceleration measurements can then be converted into energy expenditure or step counts, and provide information on time spent in different body positions (*i.e.,* sitting, lying, standing) and intensity of physical activity. Although the devices can be costly, accelerometers are non-invasive tools that are less resource-intensive than the DLW technique and provide more accurate and objective physical activity measurements in comparison to self-reports.[16,26] They are valuable for gathering wealth of detailed physical activity data in large population-based studies.[27] The new tri-axial accelerometers also show better validity than the older uni-axial design when compared to DLW measurements.[28,29] The increasing accuracy and relative ease of administration of accelerometers have led to more widespread applications of these devices in a variety of health research settings.

The downside of accelerometers is the lack of standard protocol to manage or clean the large amounts of data. The physical activity measurements can also noticeably differ based on the wear location of the accelerometers, which may require researchers to conduct a sensitivity analysis or literature review on their population of interest before deciding on the wear location of their devices. Moreover, the translation of raw acceleration to energy expenditure can vary depending on specific scoring algorithms applied by the analysis software. Similarly, the categorization of physical activity intensity is influenced by the cutpoints applied to the data.

1.2.7 Pedometers

Pedometers are another type of wearable devices like accelerometers; however, their functionality is much simpler in that pedometers are primarily used to measure step counts. Conventional pedometers have the appeal of low cost in comparison to accelerometers, while providing accurate step count data during running or walking.[30] With the recent increase in popularity, commercial pedometers also come with additional features of heart rate monitoring, global positioning system, and detection of exercise intensity similar to accelerometers or heart rate monitors. However, the accuracy of such measurements have not been fully validated in commercial products, and conventional pedometers are ineffective at detecting horizontal motion that occur during upper body movements or leisure activity.[31] While pedometers can be useful in measuring step count, they are generally limited in their ability to provide more detailed physical activity data with regards to intensity, frequency, or duration.

1.2.8 Heart rate monitors

These devices are typically worn on the wrist or chest to track patient's heart rate in real time. The data can be used to estimate energy expenditure and interpreted to reflect the frequency, duration, and intensity of one's physical activity. Heart rate monitors have the advantage of better capturing upper body movements that can be missed by accelerometers or pedometers, and are appropriate for categorizing patient's physical activity levels.[32] However, the monitors are not ideal when exact physical activity measurements are required. The non-linear relationship between heart rate and energy expenditure at low- or high-intensity physical activity also makes it difficult to accurately measure energy expenditure.[33] Moreover, heart rate measurements are confounded by patient characteristics (*e.g.,* body composition, age, gender) and factors unrelated to physical activity (*e.g.,* caffeine, stress) that can further reduce its accuracy in estimating energy expenditure.[34]

1.2.9 Selection of physical activity measurement tools

This study required accurate daily physical activity measurements in a large number of patients with fibrotic ILD. Although the DLW technique and calorimetry offered high accuracy, these methods were incompatible for studying a large group of patients in free-living conditions and hindered by their high costs. Direct observation was limited in its ability to provide objective physical activity data. In addition, data from pedometers and heart rate monitors had concerns of accuracy and lacked details regarding intensity, frequency, or duration of physical activity. Thus, the selection of tri-axial accelerometers as the primary measurement tool provided the ideal balance of accuracy, detailed and objective physical activity data, ease of administration, and cost effectiveness for this study. Accelerometry data were also supplemented with a self-report questionnaire and diary that provided more details on frequency, duration, and type of physical activity and facilitated the management of accelerometry data.

While most accelerometers are accurate at detecting step counts, ActiGraph wGT3X-BT tri-axial accelerometers were chosen over other brands (*e.g.,* Lifecorder, TracmorD, SenseWear, DynaPort) given its better performance in measuring energy expenditure.[26] The International Physical Activity long form (IPAQ-LF) was selected as the self-report to supplement the accelerometry data as it provides further information on types of activity (*e.g.,* work-related, leisure, transportation-related, housework-related) that may allow for exploratory analysis. The IPAQ-LF has also been validated against accelerometry in a multinational population.[35] Moreover, the last seven day recall of the IPAQ-LF aligned with our duration of physical activity assessment using accelerometers. The self-report log in this study was specifically designed to collect information on bed times and non-wear periods of ActiGraph monitors to facilitate the analysis of accelerometry data.

1.3 OVERVIEW OF FIBROTIC INTERSTITIAL LUNG DISEASE

Fibrotic ILDs are a group of highly morbid chronic lung conditions. Although individual diseases in this broad category differ in their prognoses and treatments, all types of fibrotic ILD are characterized by irreversible scarring of the tissues and space around the alveoli, known as the interstitium.[36] Fibrotic ILDs can also cause similar damages beyond the interstitium to affect the alveoli themselves, airways, and blood vessels surrounding the alveoli. The inflammation and accumulation of scar tissues in the lungs hinder gas exchange, which results in dyspnea, coughing, and declining lung function that lead to respiratory failure and premature death.[37] While some forms of fibrotic ILD are idiopathic, other types can be caused by environmental or occupational exposures such as cigarette smoke, asbestos, pneumotoxic drugs, or allergens.[36]

Fibrotic ILDs increase in frequency with older age and a history of smoking, with an estimated 40,000 Canadians currently living with the diagnosis.[38–40] Patients with idiopathic pulmonary fibrosis (IPF), a more progressive fibrotic ILD subtype, have a median survival of 3 to 5 years, while those with other fibrotic ILDs can expect a median survival of >10 years from the time of diagnosis.[37,41] Anti-inflammatory, anti-fibrotic, and immunosuppressive medications are commonly used for disease management. However, no curative treatment is currently available for patients with fibrotic ILD with the exception of lung transplantation, and existing pharmacotherapies are frequently associated with dose-limiting adverse effects.[42,43] With the aging population and improvements in detection and disease classification, fibrotic ILD is becoming a growing health concern due to its adverse impact on healthcare costs and quality of life in the frail and elderly population.[44]

1.3.1 Physical activity and comorbidities in fibrotic ILD

The high disease burden of fibrotic ILD renders patients out of breath or fatigued during simple activities of daily living such as walking, carrying groceries, showering, or climbing a flight of stairs. This starts a vicious cycle known as deconditioning, in which patients' discomfort associated with physical activity discourages them from engaging in any form of exertion, leading to a further decline in their lung function and functional capacity.[45] This process underscores the importance of physical activity in maintaining quality of life and slowing disease progression.[46] Despite this fact, physical activity remains low across patients with different ILD subtypes and severity.[47–49] This low level of physical activity is only partially accounted for by pulmonary symptoms of fibrotic ILD,[50] indicating other factors like extrapulmonary comorbidities may also impact physical activity.

Patients with fibrotic ILD are at an increased risk of having pulmonary comorbidities, such as lung cancer and emphysema (impaired gas exchange due to over-inflation and loss of elasticity of the alveoli), given the prevalence of smoking history.[51–54] However, extrapulmonary comorbidities are also commonly present in fibrotic ILD. Cardiovascular disease,[55,56] diabetes mellitus,[57–59] and gastro-esophageal reflux[58,60] are reported in up to 25%, 33%, and 50% of patients with IPF, respectively, with evidence that these conditions can be associated with increased mortality risk. Respiratory or lower limb muscle dysfunction and weakness are also gaining wider appreciation in respiratory conditions given their role in deconditioning that leads to poor survival and impaired quality of life.[46,61] In addition, researchers and healthcare providers are examining more overarching deficits of frailty, dyspnea, and fatigue that are implicated in ILD symptoms, other pulmonary and extrapulmonary deficits, and patient's quality of life.[62,63]

Previous studies have shown lung function and pulmonary comorbidities to be associated with reduced daily physical activity in patients with fibrotic ILD.[50,64] Cardiovascular impairments also limit exercise capacity in patients with ILD, and in fact, has stronger correlation with exercise limitation than ventilatory or gas exchange impairments.[65] This dissertation specifically focuses on how depression, anxiety, poor sleep quality, and pain affect physical activity in patients with fibrotic ILD. The impact of these four extrapulmonary deficits on quality of life and day-to-day functionality is not trivial. For example, clinically significant symptoms of depression and anxiety are present in up to 50% and 30% of patients with IPF, respectively.[66] Moderate to significant sleep disruption arising from disordered breathing has been shown to impair physical and social functioning, with growing evidence of sleep-desaturation being associated with increased mortality in ILD.[67,68] The level of pain is another factor that affects patient's quality of life and has been associated with disease severity.[66] While their effects on patient well-being has been previously explored, greater understanding is needed on how depression, anxiety, poor sleep quality, and pain impact physical activity in fibrotic ILD and the relative importance of each deficit. Thus, focusing on these four extrapulmonary comorbidities—as opposed to downstream consequences such as fatigue or frailty—addresses a novel research question and allows us to examine whether such deficits can be specifically targeted by intervention or medication to promote physical activity and improve patient outcomes in fibrotic ILD. Chapter 2 of this dissertation addresses some of these gaps in knowledge by comprehensively evaluating the association of depression, anxiety, poor sleep quality, and pain with physical activity in a large prospective cohort of patients with fibrotic ILD.

1.4 MID: DEFINITION, IMPORTANCE, AND WHAT WE KNOW IN FIBROTIC ILD

While mortality and adverse health events are important clinical outcomes, patient-reported outcomes (PROs) provide valuable insight on patient's overall wellbeing and their perspectives on benefits and harms of medical care they receive. PROs can entail any measure that patients find relevant or important to their health;[69] in keeping with the theme of this dissertation, examples of PROs in fibrotic ILD can include physical activity, depression, and pain. Various PRO instruments exist in the form of questionnaires or clinical assessments, and they are becoming commonplace in clinical trials and patient care to assess the effectiveness of interventions or medications. However, the challenge lies in interpreting the changes in PROs: researchers, healthcare providers, and patients need to be able to distinguish between noise and meaningful change in these outcome measures that can warrant an adjustment in patient management or approval of new therapy.[69]

The MID provides this vital distinction to define a magnitude of change in PROs that patients perceive as beneficial or harmful. This information is valuable to healthcare providers and patients in guiding clinical decisions. The MID also allows researchers to conduct sample size calculations to design clinical trials that are adequately powered to detect change in outcome variables. Moreover, the MID serves as a goal threshold for treatment effect that can help healthcare policy- and decision-makers in assessing novel therapy. The concept of MID has been extensively studied in diverse health conditions given its clinical value, including depression and anxiety,[70] sleep quality,[71] and pain.[72] In the context of fibrotic ILD, researchers have previously reported MIDs for general health status,[73] lung capacity and function,[73,74] and dyspnea.[75] However, no MIDs for physical activity currently exist for patients with fibrotic ILD.

Chapter 3 of this dissertation addresses this novel area by estimating the MID for moderate-to-vigorous physical activity (MVPA) in this population. While it is generally agreed that physical activity plays an important role in ILD progression and quality of life, ambiguity exists in what healthcare providers and researchers consider to be a meaningful change in patient's activity levels. Our suggestion of MID contributes to a future framework that can help healthcare providers assess improvements in patient's day-to-day functionality and effectiveness of structured exercise programs, such as pulmonary rehabilitation.

1.5 Ways to estimate MID

Two primary approaches for estimating MID in PROs are the anchor-based and distribution-based methods. While both approaches measure the change in PROs, they differ in the type of change measured and have variations within each approach.

1.5.1 Anchor-based approaches

Anchor-based approaches examine the relationship between the target PRO and other relevant outcomes (*i.e.,* anchors) to derive MID. This is typically done using a linear regression equation in which the anchor is the independent variable and the target PRO is the dependent variable.[70,75] The MID of the target PRO (*e.g.,* MVPA) can then calculated from this regression equation based on the previously established MIDs of the anchors (*e.g.,* lung capacity, quality of life score). Longitudinal data are preferred for anchor-based analysis because they allow researchers to directly examine the change in PRO of interest that corresponds to the change in anchors across two time points. Anchor-based analysis can also be applied to cross-sectional data by examining the association of the target PRO with the anchors at a single time point; however, this is not ideal as such association may not reflect true change.[76]

Different anchor-based approaches also vary in their types of anchor used. One variation evaluates the target PRO in relation to measures of diagnosis or disease severity (*e.g.,* lung capacity), while other variations relate the PRO of interest to adverse life events unrelated to the disease (*e.g.,* divorce, job loss) or global ratings of change reported by patients.[76,77] The downside to using non-disease-related anchors is that their associations with PROs are not always clear. On the other hand, only using disease-related anchors to estimate MID may be an over-simplification that fails to take into account various factors that affect PROs. Thus, it is best practice to select multiple anchors that are clinically relevant, important to patients, and at least moderately associated with the target PRO.[75] Given that this dissertation provides baseline physical activity data in our cohort, we used the cross-sectional anchor-based approach with multiple relevant anchors (*i.e.,* lung function, step count, quality of life) to estimate the MID for MVPA in patients with fibrotic ILD.

In general, anchor-based approaches have the advantage of linking the change in PRO to a meaningful external anchor. This produces MID estimates that are more generalizable to the population of interest.[75] Anchor-based methods are also able to take non-disease-related factors into consideration, which cannot be done in distribution-based analysis. However, potential non-linear relationships between the selected anchor and target PRO can complicate the analysis.[76] Moreover, no specific protocol exists for appropriate anchor selection, thus MID estimates can differ depending on which anchors are used. The anchor-based analysis also fails to take into account the measurement errors of the PRO instrument, which can produce MIDs that cannot be distinguished from random variation of the measure. Therefore, it is most ideal to supplement anchor-based estimates of MID with distribution-based analysis that takes measurement variability into consideration.

1.5.2 Distribution-based approaches

This method uses different measures of variability—notably standard error of measurement (SEM), standard deviation, effect size, minimum detectable change, or reliable index change—to derive MID. There is no single method that is clearly superior at defining the MID compared to others. The selection of measure of variability in distribution-based approach is dependent on the outcome and population of interest, PRO instrument, sample size, and study design.

SEM and standard deviation: SEM is the variation in PRO measures due to instrument unreliability. Thus, any changes in PROs that is less than the SEM are considered as measurement errors. Researchers have suggested the thresholds of 1 SEM, 1.96 SEM, and

2.77 SEM for estimating the MID.[78–80] Similarly, standard deviation is defined as the extent of variability in a group of outcome measures, with 0.5 standard deviations being commonly used to define the MID.[81,82] However, it is not always entirely clear which threshold should be used in SEM- or standard deviation-based approaches. The appropriate threshold may therefore largely depend on the reliability of the PRO instrument and variability of the measured outcome in one's sample.

Effect size: This is a standardized measure of change defined as the difference in baseline and post-treatment PRO scores divided by the standard deviation of baseline scores.[83] Again, no consensus exists on the appropriate effect size that serves as the MID; however, thresholds of 0.2, 0.5, and 0.8 effect size have been proposed to indicate small, moderate, and large changes, respectively, with 0.5 effect size being commonly used in distribution-based approaches.[75,84]

Minimum detectable change and reliable index change: Minimum detectable change is closely associated with SEM in that it is the smallest amount of change that is above the measurement error or noise at a given level of confidence.[83] It is calculated as the product of the z-score and SEM, and the MID can be defined as a change in PRO greater than this minimum detectable change.[85] The reliable index change is a related concept in which the change in individual patient's PRO score is divided by the square root of SEM. If this value is greater than 1.96, the change in PRO is considered to be a true change.[83]

Limitations and strengths of distribution-based approaches: Distribution-based MID estimates are largely dependent on the variability observed in the studied samples, which may limit the generalizability of reported findings to the overall population of interest. Some argue that the reliance on statistical significance in distribution-based results does not adequately reflect the concept of clinical significance purported by MID.[83] Moreover, the lack of consensus on which measure of variability to use leads to discrepancies in MID estimates. On the other hand, one could argue that this varied methodology is necessary and provides researchers with flexibility to account for differences in the variability of PROs, reliability of PRO instruments, and characteristics of study populations.

In addition to the cross-sectional anchor-based estimates, the 1 SEM criterion is used to define the MID for physical activity in this dissertation. Given our cross-sectional physical activity data, other distribution-based methods—which required longitudinal analysis—could not be used. The threshold of 1 SEM has also been previously used in MID studies for dyspnea, quality of life, general health status, and lung capacity in fibrotic ILD.[73,75]

1.6 SUMMARY OF THESIS

The focus of my research was to better understand the determinants of physical activity and ways to measure and interpret changes in physical activity in patients with fibrotic ILD.

Chapter 2 focuses on how extrapulmonary deficits—namely depression, anxiety, poor sleep quality, and pain—affect physical activity in fibrotic ILD. We hypothesized that these deficits would play a significant role in limiting physical activity in patients with fibrotic ILD. Additionally in chapter 3, we examined the validity of the widely used the IPAQ-LF in measuring daily physical activity and estimate the MID for MVPA in patients with fibrotic ILD.

Chapter 2: Determinants of physical activity in fibrotic ILD

2.1 Introduction

Maintenance of physical activity can prevent deconditioning in patients with fibrotic ILD,[46] which is particularly important given the absence of well-tolerated and effective pharmacotherapies for many ILD subtypes;[86–90] however, many patients with fibrotic ILD remain physically inactive.[48–50] This low level of physical activity is only partially accounted for by the pulmonary manifestations of fibrotic ILD,[50] indicating that other common extrapulmonary manifestations may also impact physical activity.

Patients with fibrotic ILD commonly have symptoms of depression and anxiety,[66,91] poor sleep quality,[67,68] and pain;[66] the extent to which these extrapulmonary symptoms interfere with physical activity is unknown. Accordingly, the purpose of this study was to conduct a comprehensive evaluation of the impact of depression, anxiety, sleep quality, and pain on daily physical activity in a cohort of patients with fibrotic ILD. We hypothesized that these extrapulmonary deficits would have a significant detrimental impact on physical activity in patients with fibrotic ILD, and that this association would be independent of ILD severity.

2.2 Methods

2.2.1 Study population

This study enrolled patients from two ILD clinics. The cohort was a convenience sample of patients who were approached during their outpatient visits at these specialized ILD clinics. Patients with fibrotic ILD that was not related to a systemic disease were eligible, including patients with idiopathic pulmonary fibrosis (IPF),[92] chronic hypersensitivity pneumonitis,[93] idiopathic nonspecific interstitial pneumonia,[94] drug-induced ILD, or unclassifiable ILD with these fibrotic ILDs comprising the differential diagnosis.[95] Patients were excluded if they had: 1) ILD secondary to a multisystem disease (*e.g.*, connective tissue disease, sarcoidosis), 2) significant extrapulmonary comorbidities (*e.g.,* cardiovascular disease), 3) impaired mobility (*e.g.*, requiring the use of a wheelchair), or 4) undergone pulmonary rehabilitation within 6 months of recruitment. Informed written consent was obtained from all patients (University of British Columbia Providence Health Care Research Ethics Board #H16-02980).

2.2.2 Physical activity measurements

Physical activity monitors: Each patient wore wrist and waist ActiGraph wGT3X-BT tri-axial accelerometers (ActiGraph Inc., Pensacola, FL.) on his or her non-dominant side for seven consecutive days. The devices were initialized with a recording frequency of 50 Hz prior to distribution. Patients were instructed to engage in their normal routines and only remove the monitors when bathing or swimming. For the purposes of this chapter, only waist activity monitor data were analyzed for its high accuracy in measuring step count.[96]

The raw acceleration data recorded on the activity monitors were summed into 60-second epochs and filtered using the ActiLife 6.13.3 software. Sleeping times and activity monitor non-wear periods were excluded prior to the analysis of patients' physical activity. Sleeping time was defined using the Cole-Kripke algorithm, with adjustments based on patients' self-reported daily logs.[97] Non-wear periods were first identified based on patient self-report in a patient diary described below. Additional non-wear periods were identified using the Choi algorithm, defined as a minimum of 90-minutes with no detected movement, with allowance of a 2-minute interval of movement in a 30-minute period to exclude any artifactual movement.[98] Data were considered valid for each day if the patient had a minimum wear time of at least 8 waking hours. The post-filtered accelerometry data were then analyzed by the ActiLife software to determine the average daily step count over the seven-day period for each patient.

This research chapter focuses on patient's physical activity that was assessed using the step count data from the waist activity monitors. Other parameters of physical activity that were measured using the wrist activity monitors and IPAQ-LF will be discussed in chapter 3.

Patient diary: Study participants completed a daily log to record their sleeping hours and the times their activity monitors were put on and taken off (e.g., for showering or swimming). These times were cross-referenced with the raw accelerometry data to most accurately identify wear and non-wear periods.

2.2.3 Extrapulmonary deficits measurements

Patients were assessed for extrapulmonary deficits at their baseline visit prior to being given the activity monitors.

Depression and anxiety: Depression and anxiety were jointly measured by the Hospital Anxiety and Depression Scale (HADS).[99] The HADS is a 14-item patient-completed questionnaire, with seven depression-related items and seven anxiety-related items. Each item is scored on a scale from 0 to 3 providing total summed scores ranging from 0 to 21 for depression and anxiety. Patients are considered "normal" if their score ranges from 0 to 7, "borderline abnormal" if the score ranges from 8 to 10, and "abnormal" if the score is 11 or above. The HADS has been validated for assessing depression and anxiety in the elderly population and in a variety of psychiatric and somatic conditions, including chronic obstructive pulmonary disease and ILD.[100–104]

Sleep quality: Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI).[105] This self-reported questionnaire consists of 19 items and includes seven component scores: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored on a scale from 0 to 3, with all items summed to produce a global PSQI score. Poor sleep quality is indicated by a global score of 5 or greater. The PSQI has been validated for evaluating self-reported sleeping problems in older men and women,[106,107] and has been used to assess sleep quality in patients with fibrotic ILD.[67,91]

Pain: The Brief Pain Inventory short form (BPI-SF) was used to measure pain.[108] The BPI-SF is a self-reported questionnaire that assesses two pain dimensions: (1) the sensory intensity and (2) the degree to which pain interferes with various aspects of life such as mood, enjoyment of life, and relations with others. A threshold of 4 was used to distinguish mild pain from moderate to severe pain as previously described.[109–113] The BPI-SF, which was originally designed to assess the level of pain in cancer patients, is also validated for assessing non-cancer pain and has been previously used in patients with fibrotic ILD.[91,114,115]

2.2.4 Other measurements of interest

Additional baseline data included patient age, sex, number of smoking pack-years, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the diffusing capacity of the lungs for carbon monoxide (DLCO).[116,117] Pulmonary function tests were included if they were conducted within 3 months of physical activity assessment. Patients were also asked to report their total years of education, current annual household income, and the number of people in their household. Mean daily temperature and hours of daylight during the physical activity monitoring period were collected through the historical archive on The Weather Channel (https://www.theweathernetwork.com/ca [accessed on December 20-23, 2017]) and National Research Council Canada (https://www.nrc-cnrc.gc.ca/eng/services/sunrise/index.html [accessed on December 20-23, 2017]).

2.2.5 Statistical analysis

A sample size calculation identified the need for recruitment of approximately 100 patients in order to provide 90% power to detect a minimum increase of R^2 from 0.3 to 0.4 with addition of extrapulmonary deficits to a baseline multivariable model that included age, sex, and lung function as predictors of physical activity. The R^2 values used in the sample size calculation were based on a previous study in physical activity of patients with chronic obstructive pulmonary disease.[118] (**Appendix A**)

Data are described using mean±standard deviation (SD) or median (interquartile range [IQR]). Wilcoxon rank sum or Spearman correlation were used to examine the unadjusted relationship of daily step count with age, sex, smoking pack-years, ILD subtype, lung function, and extrapulmonary deficits. Multivariable linear regression models were used to determine whether each deficit independently predicted daily step count when adjusting for potential confounders that were correlated ($p<0.05$) with daily step count. Key variables were forced into the model based on their clinical relevance and likelihood of affecting general activity and quality of life, including age, sex, number of pack-years, ILD subtype, and average temperature and hours of daylight over the one-week period of physical activity monitoring. In addition, an exploratory analysis was conducted using forward selection and backward elimination stepwise regression to build a predictive multivariable model for daily step count in patients with fibrotic ILD. All statistical analysis was performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 Results

2.3.1 Study population

One hundred and fourteen patients with fibrotic ILD were recruited, including 39 with IPF. Three patients dropped out of the study prior to completing a week of physical activity monitoring, resulting in a final cohort of 111 patients. On average, patients had mild and moderate reductions in their FVC and DLCO %-predicted, respectively (**Table 1**).

2.3.2 Baseline physical activity and extrapulmonary deficits

The daily step counts measured by the waist ActiGraph activity monitors showed a right-skewed distribution with a mean of 4,920±3,590 steps/day and a median of 3,848 steps/day (IQR 2,234-6,682 steps/day). Step count was highly variable, with minimum and maximum steps in a single day of 449 and 17,005, respectively (**Figure 1**). The mean step count on weekdays was greater than the mean step count on weekends, with the mean within-patient difference showing borderline significance (351 steps, p=0.05). Patients with IPF had fewer step counts compared to those with non-IPF ILDs; however, this was not statistically significant (median 3,451 *vs.* 4,202 steps/day, p=0.19).

Sixty-seven percent of the cohort had at least one clinically meaningful measured extrapulmonary deficit. Borderline or abnormal depression and anxiety scores were present in 19% and 22% of patients, respectively. Sixty-one percent of the cohort had poor sleep quality. Moderate to severe pain was present in 12% of patients, with a mean pain interference score of 1.5±2.0 on a ten-point scale. The most frequently reported areas of pain were back (34%) and lower limbs (25%). Sixteen percent of the patients reported having pain in other areas such as their neck, chest, and upper limbs, while 24% of the cohort did not have any pain at the time of assessment. Questionnaire scores for depression, anxiety, sleep quality, and pain were similar and the prevalence of clinically meaningful deficits did not significantly differ between IPF and non-IPF patients (**Figure 2 and Table 1**). However, women were significantly more likely to have poor sleep quality (p=0.01) or moderate-to-severe pain (p=0.01) than male patients with fibrotic ILD.

2.3.3 Association of extrapulmonary deficits and physical activity

The associations of extrapulmonary deficits with daily step count are shown in **Table 2**. Higher depression scores were more strongly associated with lower step count in patients with IPF. On the other hand, sleep quality scores showed stronger correlation with physical activity in patients with non-IPF ILDs. Pain affected both IPF and non-IPF cohorts similarly and anxiety scores were not associated with daily step count in either cohort. A similar trend was observed when we categorized patients by their DLCO %-predicted values (*i.e.,* less than or greater or equal to 50%). Depression and pain scores were moderately correlated with daily step count on unadjusted analysis. Patients with scores suggestive of clinically meaningful depression or moderate to severe pain took fewer daily steps (p=0.001 and p=0.05, respectively) compared to patients with scores in the normal or mild range (**Figure 3**). No specific pain location was associated with lower step count. Patients with more extrapulmonary deficits had fewer average daily step counts (**Figure 4**).

Depression, anxiety, sleep quality, and pain severity and interference did not independently predict daily step count when each correlation was adjusted for age, sex, ILD subtype, ILD severity, and mean daily temperature and hours of daylight (**Table 3**). When a backward stepwise elimination approach was used, older age, lower FVC, lower DLCO, and higher pain severity score independently predicted fewer daily step counts (**Table 4**). This multivariable model explained a small amount of the variability in daily step count, with an R^2 value of 0.35.

2.4 DISCUSSION

Our study shows that clinically meaningful depression, anxiety, poor sleep quality, and pain are common in patients with fibrotic ILD. These deficits were common in both IPF and non-IPF ILDs, and the similar prevalence of depression and anxiety in our cohort compared to previous studies serves to validate these findings.[91,119] Although depression and pain severity were moderately associated with daily step count on unadjusted analyses, these deficits are unlikely to be primary determinants of physical activity based on the lack of independent association with adjustment for basic demographics and ILD severity.

We used daily step count as the primary physical activity measure because it is a simple metric that is easily interpretable and quantifiable, while also being readily compared across patients and to other cohorts. We chose waist activity monitors over wrist-based monitors because the latter are susceptible to incorrectly counting upper body movements as steps, and can overestimate the number of daily steps.[96] Previous studies have also used questionnaires to estimate physical activity. These are simpler to use and less burdensome compared to a device that must be worn throughout the day. However, physical activity questionnaires are subjective and prone to significant inter-observer variability that limits their use when accurate physical activity assessment is required, as in our study. Using the robust measurements acquired from a tri-axial physical activity monitor worn for a full week, we unsurprisingly found that physical activity was reduced in patients with fibrotic ILD. The mean of 4,920 steps/day is similar to a recent Japanese IPF cohort,[120] and substantially lower than the mean of 7,100 steps/day observed in healthy older populations.[121]

The prevalence of clinically meaningful symptoms of depression and anxiety,[122–124] poor sleep quality,[125] and pain[126] in patients with fibrotic ILD was similar or higher compared to the rate found in community dwelling adults in Canada or the US. This high prevalence of extrapulmonary deficits in fibrotic ILD indicates the need for healthcare providers, caregivers, and patients to pay greater attention to these potential deficits and to implement strategies to minimize their impact on the patient's quality of life, independence, and prognosis. Specifically, depression—in addition to impaired lung function—may have a greater impact on activity levels of patients with more advanced ILD or IPF. Thus, comprehensive care that rigorously targets both pulmonary and extrapulmonary manifestations of ILD may be especially beneficial for patients with more severe illnesses, and for elderly and frail individuals or those experiencing intolerable side effects from medication. However, our data also suggest that poor sleep quality and pain should still be addressed in patients with milder disease, given the impact of these deficits across disease subtype and severity. Previous research has also shown that depression, anxiety, and sleep disturbances can lead to poor medication adherence in the elderly population or patients with multiple chronic diseases.[127–129] Thus, an earlier detection and treatment of these deficits may also improve adherence to medications that can preserve lung function and potentially prolong survival. Conversely, potential ILD therapies may be less effective in patients who have concurrent extrapulmonary deficits. In this situation, it may be beneficial to aggressively manage the extrapulmonary deficit in order to allow maximal benefit to be achieved from interventions like pulmonary rehabilitation.

Depression and pain were moderately correlated with lower physical activity on unadjusted analysis, although pain was retained in the exploratory stepwise regression model. This novel finding indicates that pain may be an important and potentially modifiable determinant of physical activity in fibrotic ILD, similar to emerging literature that show pain to be associated with lower physical activity in patients with chronic obstructive pulmonary disease.[109,130] Our finding may suggest that interventions targeting physical activity (*e.g.*, pulmonary rehabilitation) should place more emphasis on how patients with fibrotic ILD are impacted by pain.

However, the results of this stepwise regression model is hindered by the issue of multicollinearity. Given that many of the extrapulmonary deficits were highly correlated with each other, the inclusion of depression, anxiety, sleep quality, and pain scores into a single model reduces the statistical significance of each deficit on physical activity. Thus, the final stepwise regression model may not accurately represent the impact of extrapulmonary deficits on physical activity, and was mostly done as a hypothesis-generating analysis. In fact, when we transformed extrapulmonary deficits scores using principal components analysis, the final models for both forward selection and backward elimination approaches only showed age, FVC and DLCO %-predicted, and income to be independent predictors of physical activity.

Due to this concern with multicollinearity and largely exploratory nature of the stepwise regression model, we used the forced multivariable approach as our primary analysis. This allowed us to create a separate statistical model for each extrapulmonary deficit; the variance inflation factors of all predictor variables in these models were less than 4, suggesting that multicollinearity did not significantly impact the statistical relationship between extrapulmonary deficits and step count. However, it should be acknowledged that the cause and effect are not entirely clear in either stepwise regression and forced multivariable approach. While we present our data to suggest that extrapulmonary deficits lead to lower physical activity, one could reasonably argue that reduced levels of activity lead to worse extrapulmonary deficits. Moreover, there may exist a relationship among extrapulmonary deficits (*e.g.,* patients with chronic pain may be more depressed) and analyzing these deficits separately may be an oversimplification of how physical activity is influenced by various factors. Such limitations of our study indicate the need for future studies to investigate how certain extrapulmonary deficits serve as mediator variables for other comorbidities. While our preliminary analysis suggests that the interaction of multiple deficits does not result in a significantly lower step count compared to patients with individual deficits, future work with larger cohorts could also explore the impact of disease burden on physical activity. In addition, the large variability in daily step count and the relatively low R^2 value suggest that physical activity is not entirely accounted for by pulmonary and extrapulmonary manifestations. Additional factors (*e.g.*, lifestyle, patient motivation, quality of life) may explain this variability and should be explored in future studies. Although our findings indicate that extrapulmonary deficits play a limited role in physical activity, these could still be determinants of other important outcomes in fibrotic ILD such as dyspnea, health-related quality of life and mortality. These questions were beyond the scope of this study, but are important topics for future larger cohorts that have a longer duration of follow-up.

2.5 CONCLUSIONS

In summary, we show in our cohort of patients with fibrotic ILD that physical activity is reduced compared to a general older adult population and that extrapulmonary deficits (depression, anxiety, poor sleep quality, and pain) are common but have a small impact on physical activity. Additional studies are required to determine whether extrapulmonary deficits are modifiable targets for therapies, and whether they are potential determinants of health-related quality of life, medication adherence, and prognosis.

Chapter 3: Minimally important difference for physical activity and validity of the International Physical Activity Questionnaire in fibrotic ILD

3.1 Introduction

The most important outcomes in patients with chronic illness include how they feel, function and survive. In patients with ILD, physical functioning is intricately related to how they feel and is a major determinant of quality of life.[46,131,45] A valid measure of physical activity would yield meaningful information about ILD disease status and could be a useful metric to evaluate effectiveness of therapeutic interventions, assess disease progression, and estimate prognosis.[46,131,132] Doubly labeled water and accelerometry are the current reference standards for measuring physical activity;[3,133] however, both are resource-intensive. The six-minute walk test is frequently used as a measure of physical functioning, but in patients with ILD, it is best regarded as a measure of submaximal (or maximal) exercise and is a poor reflection of physical activity in daily living.[134,135]

Self-reported questionnaires are simple to administer and can yield information on a range of outcomes meaningful to patients. Given the importance of daily physical activity for patients with ILD and the simplicity and potential benefits of the self-report method to collect outcome data, a self-report measure of physical activity could be particularly useful in the assessment and monitoring of patients with ILD. The IPAQ is a questionnaire that asks patients to report the duration and frequency of physical activity in various domains within the last seven days.[11] The IPAQ has been shown to be reliable and valid in a large multinational sample,[133] and has been used in multiple healthy or chronic disease populations, including patients with IPF.[45,35,136] However, its performance characteristics have not been assessed in more heterogeneous samples of fibrotic ILD. To address this gap, our primary objective was to determine the validity and internal consistency of the IPAQ-LF in measuring physical activity in patients with fibrotic ILD in comparison to tri-axial accelerometry. Our secondary objective was to estimate the MID for MVPA as measured by the IPAQ-LF and accelerometer.

3.2 METHODS

3.2.1 Study overview

Patients with fibrotic ILD were recruited from two specialized ILD clinics between December 2016 and September 2017 after providing written informed consent (University of British Columbia Providence Health Care Research Ethics Board #H16-02980). The cohort was a convenience sample of eligible outpatients who were identified during routine clinical visits. Patients wore waist and wrist ActiGraph activity monitors for seven consecutive days, and were instructed to complete the IPAQ-LF at the end of the seven-day period as described below; the activity monitors and paper questionnaires were returned by mail. A single follow-up visit was completed 6±2 months after the baseline visit, with patients completing the same study measurements in the same order.

3.2.2 Study population

The same cohort of patients from chapter 2 were used for this analysis. The study population included patients with fibrotic ILDs that have manifestations limited to the lungs (*i.e.,* IPF,[92] chronic hypersensitivity pneumonitis,[93] idiopathic nonspecific interstitial pneumonia,[94] drug-induced ILD, or unclassifiable ILD with these fibrotic ILDs comprising the differential diagnosis[95]). Patients were excluded if they had significant extrapulmonary disease that impaired physical activity or had undergone pulmonary rehabilitation within 6 months of study enrolment.

3.2.3 Physical activity questionnaire

The IPAQ-LF was completed by self-report after wearing the ActiGraph activity monitor for seven consecutive days. This questionnaire includes 27 items that has been validated against waist activity monitors in a general middle-aged population.[35] These items assess the amount and intensity of physical activity in domains relating to occupation, transportation, housework, and recreation. Patient-reported minutes per day spent in different intensities of activity (walking, moderate, and vigorous) were summed to determine the total minutes per week for each type of activity. These minutes were then multiplied by a pre-specified constant according to their intensity levels to provide a continuous score expressed in metabolic equivalent of task (MET)-minutes/week. As previously described,[11] walking, moderate, and vigorous activity minutes were multiplied by constants of 3.3, 4.0, and 8.0, respectively, with the exceptions of moderate housework-related activity inside the home and vigorous housework-related activity that used constants of 3.0 and 5.5, respectively and minutes of transportation-related cycling that was multiplied by a constant of 6.0. Patients provided the number of minutes/day of MVPA, which generally consists of activities that require more exertion than transportation-related or casual walking (*e.g.*, carrying light loads, heavy lifting, running, cycling). Patients also reported the numbers of hours spent sitting or lying during waking hours on a usual weekday and weekend day. The weighted average of these self-reported hours was used to determine daily sedentary time during waking hours as described in the IPAQ guidelines.[11] In addition, we estimated patient's weekly inactive time by subtracting the combined weekly minutes of walking, moderate, and vigorous activities from the total minutes in a week.

3.2.4 Physical activity monitor

As previously described in chapter 2, all patients wore waist- and wrist-based ActiGraph wGT3X-BT tri-axial accelerometers (ActiGraph Inc., Pensacola, FL.) on their non-dominant side for seven consecutive days. The devices were initialized with a recording frequency of 50 Hz prior to distribution. Patients were instructed to engage in their normal routines and only remove the monitors when bathing or swimming. Sleeping times and non-wear periods were excluded. The former was defined using the Cole-Kripke algorithm, with adjustments based on patients' self-reported daily logs.[97] Non-wear periods were first identified based on patient self-report in the daily log and further refined using the Choi algorithm. This algorithm defines non-wear periods as a minimum of 90 minutes with no detected movement, allowing up to two minutes of movement per 30-minute period to exclude any artifacts.[98] Physical activity data were considered to be valid for each day if the patient had a minimum wear time of 8 waking hours.

All 7 days of raw data were downloaded with and without an added sensitivity filter (low frequency extension [LFE]). The data were summed and filtered by the ActiLife 6.13.3 software to determine the average daily step count and sedentary time for each patient. In addition, the software employed previously established algorithms and cut-off points to calculate weekly MVPA minutes and activity-related energy expenditure. Freedson Adult VM3 thresholds were used to categorize activity intensity as moderate, vigorous, and very vigorous;[137] MVPA was defined as activity intensity ranging from 'moderate' to 'very vigorous.' Energy expenditure was calculated for each patient using the Freedson VM3 algorithm as the total activity-related kilocalories spent over the 7-day period.[137] The total activity-related kcal was divided by the patient's weight and hours of activity monitor wear time (excluding sleep) to convert to total MET-minutes/week. Lastly, the total inactive time for each patient was calculated as the sum of the total sleeping and sedentary time over the 7-day period.

3.2.5 Additional measurements

Age, sex, number of smoking pack-years, and pulmonary physiology measurements were obtained from the patient chart. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and diffusing capacity of the lungs for carbon monoxide (DLCO) were measured at routine clinical visits according to standard recommendations.[116,117] The European Quality of Life 5-Dimensions 5-level version (EQ-5D)[138–140] was used to measure health-related quality of life, with index scores derived from a Canadian population.[141] Baseline data were included if obtained within 3 months of study enrolment.

3.2.6 Statistical analysis

Internal consistency and validity of IPAQ-LF: The internal consistency of the questionnaire was determined using Cronbach's alpha. The validity of the IPAQ-LF was tested using Spearman rank correlations by comparing the IPAQ-LF estimates of the average daily sedentary time, weekly MVPA minutes, and weekly energy expenditure with the corresponding measures from activity monitors and relevant clinical outcomes, including FVC and DLCO %-predicted, daily step count, and EQ-5D index score.

Calculation of MID for MVPA: We used anchor- and distribution-based methods to calculate the MID for weekly MVPA minutes as estimated by the IPAQ-LF and waist activity monitor. FVC %-predicted, daily step count, and EQ-5D index score were chosen as anchors for MID analysis using IPAQ-LF data based on their moderate-to-strong correlation (*r*≥0.30) with weekly MVPA minutes, frequent use, and clinical relevance. Similarly, FVC and DLCO %-predicted and EQ-5D index score were selected as anchors for determining the MID for MVPA measured by waist activity monitor without LFE.

We used linear regression to examine associations between the outcome (*i.e.*, MVPA minutes according to the IPAQ-LF and waist activity monitor) and the anchors.[142,70] Based on these regression equations, we generated the lower and upper limits of the MID for weekly MVPA minutes that corresponded to a previously reported range of MID for each anchor, using ILD-specific data where available. We used a MID range of 2 to 6% for FVC in an IPF population,[74] a range of 600 to 1,100 steps/day that was reported in a different COPD cohort,[143] and a range of 0.037 to 0.069 for EQ-5D index score that was determined from a general Canadian population.[144] Given the absence of an established MID for DLCO in ILD, we used a range of 10-14% as meaningful change based on clinical impression and the association of DLCO with functional capacity in chronic lung disease.[145]

Although there are numerous approaches for the distribution-based method, we used one-half the baseline standard deviation and the standard error of measurement (SEM) criteria to define MID.[81] The SEM is calculated by multiplying the standard deviation of weekly MVPA minutes by the square root of 1 minus the measure of internal consistency (*i.e.,* Cronbach's alpha).[146,78,83] The internal consistency of the IPAQ-LF was determined as described above; the Cronbach's alpha value of the activity monitor was based on the correlations among its physical activity measurements (*i.e.,* MVPA minutes, energy expenditure, step count, sedentary time, and inactive time). Analyses were repeated stratifying for IPF and non-IPF diagnoses. All statistical analysis was performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

3.3 RESULTS

3.3.1 Study patients

One hundred and fourteen patients with fibrotic ILD were enrolled, including 39 with IPF. Three patients dropped out of the study prior to completing a week of physical activity monitoring, resulting in a final cohort of 111 patients. On average, the final cohort had mild and moderate reductions in their FVC and DLCO %-predicted, respectively. Patients with IPF were more likely to be male, have a history of smoking, and have lower DLCO %-predicted compared to patients with non-IPF ILD. The demographics and lung function of the study cohort are summarized in **Table 1**.

3.3.2 Baseline physical activity

All patients met a pre-defined minimum wear time threshold of at least 8 waking hours per day. The average wear times of waist and wrist activity monitors during waking hours were 6,207±583 and 6,213±577 minutes/week, respectively. The weekly MVPA minutes, activity-related energy expenditure, sedentary time and inactive time are summarized in **Figure 5** and **Table 5**. Waist activity monitors and IPAQ-LF recorded similar findings for all measurements with the exception of weekly inactive time, which was significantly higher in the IPAQ-LF. Wrist activity monitors were more variable and on average suggested a significantly higher amount of physical activity and significantly less sedentary time compared to IPAQ-LF estimates and waist activity monitor measurements. Daily step count was also higher for wrist monitors and with use of the LFE filter (p<0.001 for all comparisons).

There were no statistically significant differences in physical activity comparing patients with IPF to those with non-IPF ILDs, excluding higher sedentary time in IPF when using waist activity monitor measurements (**Appendix B**). Patients with IPF had fewer weekly MVPA minutes reported in the IPAQ-LF and had higher inactive time measured by the activity monitor compared to patients with non-IPF ILDs, with borderline significance. A detailed breakdown of the IPAQ-LF data is provided in **Appendix C**.

3.3.3 Internal consistency and validity of the IPAQ-LF

The internal consistency of the IPAQ-LF assessed by Cronbach's alpha was 0.78. Physical activity data from the waist activity monitor without LFE was used as the reference standard to assess the validity of the IPAQ-LF. The IPAQ-LF estimates of energy expenditure, sedentary time, and inactive time mostly showed moderate-to-strong correlations with accelerometry data; however, self-reported weekly MVPA minutes of the IPAQ-LF was weakly correlated with the corresponding measurements from waist activity monitor (Table 6). The same four parameters of the IPAQ-LF generally showed moderate-to-strong correlations with relevant clinical outcomes, with the exception of self-reported sedentary time that showed no meaningful relationship with FVC and DLCO %-predicted (Table 7).

On average, patients over-reported their weekly MVPA, energy expenditure, sedentary time, and inactive time in the IPAQ-LF relative to waist activity monitor measurements; however, the difference in measurements of the IPAQ-LF and activity monitor was mostly within the limits of agreement. Patients with higher levels of physical activity were more likely to over-report their weekly MVPA and energy expenditure compared to patients with lower levels of activity. (**Figure 6**)

3.3.4 Estimation of MID for MVPA

The MID ranges for MVPA measured by the waist activity monitor without LFE and IPAQ-LF were 8-74 and 13-58 minutes/week, respectively, while the distribution-based MID ranged from 69-242 minutes/week (**Table 8**). In a subgroup analysis, the anchor-based MID for MVPA measured by the activity monitor and IPAQ-LF in patients with IPF were 12-101 and 13-62 minutes/week, respectively. This range was much higher in the distribution-based approach, in which the MID was 84-204 minutes/week of MVPA. The anchor-based MVPA MID for patients with non-IPF ILDs were 7-64 and 8-65 minutes/week when using the activity monitor and IPAQ-LF data, respectively, while the distribution-based MID was 60-258 minutes/week. A lack of significant changes in physical activity and clinical variables over 6 months of follow-up prohibited longitudinal MID analysis. (**Appendix D**)

3.4 DISCUSSION

We used a cohort of 111 patients with fibrotic ILD to demonstrate the validity and internal consistency of the IPAQ-LF and to estimate the MID for MVPA. These findings have important implications for both patients and clinical researchers, identifying simple and accurate methods of recording physical activity and providing tangible goals for physical activity programs and clinical trials.

The IPAQ-LF has acceptable internal consistency for use in patients with fibrotic ILD, indicating that different questionnaire items are reliably measuring the same construct of physical activity without being redundant. Although absolute measurements differed between the IPAQ-LF and waist activity monitor, this difference was not clinically significant for majority of patients. In addition, most IPAQ-LF parameters showed moderate-to-strong correlations with corresponding accelerometry data and relevant clinical outcomes. While it is premature to confirm or prove validity, our finding suggest that the IPAQ-LF may be a simple tool that can provide a reasonable estimate of physical activity and sedentary behavior that show a meaningful relationship with relevant clinical outcomes such as disease severity and quality of life in patients with fibrotic ILD.

However, healthcare providers and researchers may need to be mindful in using the IPAQ-LF for patients that lead an active lifestyle as there is a greater tendency for such patients to over-report their activity levels. Moreover, the current IPAQ guideline only assesses sedentary behaviour during waking hours. This exclusion of sleeping time may provide an inaccurate representation of patient's general level of inactivity throughout the day, especially in patients with fibrotic ILD that spend many hours in bed. To account for this, we calculated the weekly inactive time by subtracting the total self-reported minutes of activity in the IPAQ-LF from the total minutes in a week. Our analysis shows that using this comprehensive measure allows IPAQ-LF to capture patient's inactivity that is better correlated with relevant clinical outcomes.

While disease progression can be tracked and prognosis estimated through various clinical parameters (*e.g.*, pulmonary function tests, 6-minute walk test, 4-minute gait speed), such tests require specific equipment and trained personnel. The IPAQ-LF has the potential to rapidly and reliably assess physical activity, and has several advantages compared to these other measures for patients with ILD. First, clinical improvements in lung function or exercise capacity do not necessarily translate to improvements in physical functioning, and a more direct measure of physical activity and patient independence is needed. Second, IPAQ-LF is less burdensome for patients as it requires less time and resources to complete. Finally, physical activity data is more interpretable for patients compared to spirometry measurements. Thus, the IPAQ-LF can be a useful additional measure to track patient independence and quality of life.

Each patient wore both waist and wrist activity monitors throughout the study, but we focused on the waist monitors without the added sensitivity filter for most analyses given concerns about the validity of the alternatives. Both wrist monitors and the added sensitivity filter appeared to be overly sensitive to upper body movements and produced physical activity data (*e.g.*, step counts, weekly MVPA minutes) that were unreasonably high for a chronically ill and older population. In addition, the data from waist monitors without a sensitivity filter were comparable to previous reported physical activity in cohorts of patients with IPF and were similar to results obtained from the IPAQ-LF.[48,120] Together, these findings suggest that waist monitors without sensitivity filters should be the preferred option for measuring daily physical activity in patients with fibrotic ILD when accuracy and comparability over time or to other patients is important.

Our study is the first to provide an estimate of the MID for MVPA in patients with fibrotic ILD. We calculated the upper threshold for meaningful change in MVPA to be 60-75 minutes/week that corresponds to previously reported MIDs of selected anchors. We provided a range for the MID given the absence of a single MID point estimate for these anchors. The range also illustrates that a meaningful improvement in physical activity can vary among individual patients based on their disease severity, baseline activity level, quality of life, lifestyle, and motivation. It should be noted however, that the upper threshold of 60-75 minutes/week may be an overestimation of MID for MVPA, partly due to the use of DLCO as one of the anchors in our analysis for activity monitor data. While most of our anchor-based results suggest an MVPA MID of 30-40 minutes/week, the upper limit of 14% for DLCO MID leads to a higher estimate of 75 minutes/week. We believe that a more appropriate MID for DLCO may range from 5 to <10% based on clinical impression, which would produce an MID for MVPA that shows better agreement with other selected anchors. Thus, we suggest that an additional MVPA of 30-40 minutes/week may be sufficient for most patients with fibrotic ILD to achieve noticeable benefits.

We also calculated a distribution-based MID for MVPA, which was noticeably higher than the anchor-based estimate. This larger value is predominantly secondary to the large variability in self-reported MVPA minutes of the IPAQ-LF, and the distribution-based method therefore likely provides an overestimate of the MID for MVPA. Moreover, the distribution-based MID is less generalizable to other fibrotic ILD cohorts as it is directly dependent upon the variability of MVPA among our patients.[83] Furthermore, this higher value is less realistic given the expectation that the MID would not exceed the baseline amount of MVPA already performed and the current recommendation of 150 MVPA minutes/week.[149] We therefore believe the most appropriate MID for MVPA in patients with fibrotic ILD to be 30-40 minutes/week based on our anchor-based analysis.

Establishing an MID for MVPA is necessary to assess whether specific interventions are effective, and also provides patients with a tangible goal for their own self-directed exercise programs. Having such a goal can help motivate patients to stay active, prevent deconditioning, and maintain quality of life and independence. Moreover, there is a lack of physical activity guidelines for patients with chronic respiratory disease, and additional data are needed to support the development of evidence-based recommendations. Other cohorts of patients with ILD or COPD display similar physical activity profiles, with weekly MVPA of 100-200 minutes and daily step count of 3,000-4,000. These similarities suggest physical activity recommendations could be applied to a wide variety of older patients with chronic lung diseases.[143,147,148,49,120]

The primary limitation of our study was the use of a single cohort without an external validation group. In addition, some of the anchors used in the MID analysis were not based on a fibrotic ILD population, and we were unable to conduct a longitudinal analysis of MID for MVPA due to the lack of significant change in physical activity and clinical outcomes after 6 months. Thus, our derivation of MID with cross-sectional data may not reflect the true association between changes in anchors and physical activity in fibrotic ILD. These issues indicate the need to replicate these findings in other populations; however, our key findings are strengthened by the relatively large sample size of 111 patients who had similar baseline features compared to other ILD cohorts and the similar findings in IPF and non-IPF subgroups. We therefore believe that our results on the IPAQ-LF validity and MID estimates are likely applicable to a broader population of patients with fibrotic ILD.

3.5 Conclusions

In summary, we used a large cohort of patients with fibrotic ILD to show that the IPAQ-LF has acceptable validity and internal consistency for the assessment of daily physical activity when compared to objective activity monitor data and relevant clinical outcomes. We also provide an estimate of the MID for MVPA using anchor- and distribution-based methods that provides a goal threshold of effect for future clinical trials and for patients engaged in formal or self-directed exercise programs. Importantly, we show that adding only 30-40 minutes of MVPA per week is a realistic goal that can have a noticeable benefit to patients with fibrotic ILD.

Chapter 4: Conclusions

In this dissertation, I presented two research chapters on physical activity in fibrotic ILD. Our work was the first to comprehensively evaluate the impact of multiple extrapulmonary deficits on daily physical activity, assess the validity and internal consistency of the IPAQ-LF, and provide an MID for MVPA in the context of fibrotic ILD.

While extrapulmonary deficits had limited impact on maintenance of physical activity, we report that depression, anxiety, poor sleep quality, and pain are prevalent in patients with fibrotic ILD. The high prevalence of extrapulmonary deficits indicates the need for healthcare providers to screen for and treat extrapulmonary deficits more rigorously to minimize the impact of these deficits on patient's quality of life, independence, and prognosis. It is also important to raise awareness and provide education for patients and their caregivers to discuss such issues earlier on with their healthcare providers in order to implement strategies to address these deficits. This could be especially beneficial for elderly and frail patients, those experiencing intolerable side effects from medication, and patients with advanced ILD who carry a high physiological and psychological burden of illness. Moreover, timely management of depression, anxiety, and sleep disturbances may improve adherence to medications that preserve lung function and potentially prolong survival. Our findings also suggest pain as a potential modifiable determinant of physical activity in patients with fibrotic ILD. Interventions that target physical activity, such as pulmonary rehabilitation, could implement strategies to better address pain in patients by incorporating low-stress exercises that is able to achieve the required exercise intensity without aggravating painful sites, referrals to pain specialists, or prescription of appropriate pain medication. With similar emerging literature on the effect of pain on physical activity in COPD, it may be warranted to explore more deeply into how pain affects patients with chronic respiratory conditions.

In addition to highlighting the prevalence and potential impact of extrapulmonary deficits, our work also confirmed that physical activity is reduced in patients with fibrotic ILD compared to a healthy older adult population. This underscores the need to better communicate the importance of physical activity to patients and their caregivers, while healthcare providers need to more aggressively target improvements in physical activity through interventions like pulmonary rehabilitation. For patients without access to such services, healthcare providers could prescribe simple exercises that can be safely performed at home without specific equipment. It would also be reasonable to address barriers to increasing access to pulmonary rehabilitation by hiring and training more staff and allotting more designated staff time to deliver the intervention to patients.[150]

In the second half of this dissertation, we show that the IPAQ-LF has acceptable internal consistency and provides reasonable estimates for measuring daily physical activity in patients with fibrotic ILD. We suggest the possibility of incorporating the IPAQ-LF as an additional clinical tool that can be easily used by patients and healthcare providers alike. In addition to being less burdensome and more economical than activity monitors or other clinical assessments, the IPAQ-LF could be completed before and after an intervention to assess improvements in daily physical activity. The IPAQ-LF also provides real-world data of patient's physical activity for healthcare providers and these data can be more interpretable for patients compared to other clinical measurements. Lastly, we provide an estimate of the MID for MVPA in patients with fibrotic ILD. Such information can be valuable in assessing the effectiveness of specific interventions or medication and setting a goal threshold of effect for future clinical trials. Moreover, the MID of 30-40 minutes/week provides patients with a tangible and realistic goal to improve their physical activity to maintain their quality of life and independence. Given the similarities in physical activity profiles of other ILD and COPD cohorts, our results may be applicable to the general fibrotic ILD population and contribute to the establishment of physical activity recommendations for patients with chronic lung diseases.

We conducted a six-month follow-up for the majority of our patients; however, the lack of significant change in physical activity or extrapulmonary deficits makes it difficult to assess potential factors related to changing activity level. Future studies could benefit from having a larger cohort with a longer duration for follow-up, which could allow for more rigorous subgroup analysis and substantial longitudinal data. It would also be valuable to expand our study to compare the physical activity profiles of patients with fibrotic and non-fibrotic ILDs and examine whether targeted treatment of extrapulmonary deficits (*e.g.,* anti-depressants, pain medication) promote physical activity. Given the critical role of physical activity in deconditioning, healthcare providers and researchers could also examine the feasibility of exercise prescription in patients that do not have access to pulmonary rehabilitation, adherence to such self-directed exercise guides, and the association of this intervention with patient outcomes. Lastly, future work could include a more extensive discussion of MIDs for other physical activity parameters (*e.g.,* step count, energy expenditure, sedentary time) and extrapulmonary comorbidities in fibrotic ILD.

In summary, this dissertation presents one of the largest prospective cohort studies to assess physical activity, comprehensively examining extrapulmonary deficits in patients with fibrotic ILD. These important data provide the framework for future studies related to physical activity in fibrotic ILD and other chronic lung diseases. We also contribute to the growing knowledge of MIDs for PROs in fibrotic ILD that will be valuable in understanding the complexities of ILD management and the design of future clinical trials.

Tables

Table 1. Baseline patient characteristics.

Variable	Mean±SD or n (%)		
	Combined cohort (n=111)	**IPF (n=39)**	**Non-IPF (n=72)**
Age, years	69.9±9.4	71.2±6.7	69.3±10.6
Male sex	69 (62%)	31 (79%)	38 (53%)
Ever-smoker	76 (68%)	32 (82%)	44 (61%)
Smoking pack-years (IQR)	17.0 (0-27)	21.5 (2-37)	14.0 (0-23)
Body mass index, kg/m^2	28.8±4.8	28.8±4.6	28.8±4.9
FVC, %-predicted	76.9±19.0	74.8±17.7	77.9±19.8
DLCO, %-predicted	50.8±16.2	46.2±15.5	53.5±16.1
Depression (HADS) *	4.5±3.7	4.9±3.7	4.4±3.6
Anxiety (HADS) *	4.9±3.4	4.8±3.1	5.0±3.6
Sleep quality (PSQI) *	6.0±3.5	5.2±3.4	6.5±3.6
Pain severity (BPI-SF) *	1.9±1.8	1.7±1.6	2.1±2.0
Pain interference (BPI-SF) *	1.5±2.0	1.4±2.2	1.6±1.9
Total education, years	14.0±3.6	13.8±2.7	14.1±4.1
Family size	2.3±1.3	2.4±1.3	2.3±1.3
Annual household income			
<$25,000/year	26 (23%)	8 (21%)	18 (25%)
$25,000-50,000/year	28 (25%)	12 (31%)	16 (22%)
$50,000-100,000/year	38 (34%)	14 (36%)	24 (33%)
>$100,000/year	18 (16%)	5 (13%)	13 (18%)
Daily step count			
Mean±SD	4,920±3,590	4,563±3717	5,116±3,530
Median (IQR)	3,853 (2,236-6,805)	3,451 (1,622-6,505)	4,202 (2,693-6,805)

* Depression, anxiety, and sleep quality were scored on a 21-point scale. Pain symptoms were scored on a ten-point scale; greater scores indicate more severe symptoms.

† One patient declined to provide information on years of education, family size, and annual income.

Abbreviations: BPI-SF, Brief Pain Inventory short form; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

Table 2. Correlates of daily step count. Spearman rank correlations with p-values in brackets are shown below. The Wilcoxon rank sum test was used to examine the association of daily step count with male sex and smoking status. The relationship of annual household income and step count was examined with the Kruskal-Wallis test.

Variables	Combined cohort (n=111)	IPF (n=39)	Non-IPF (n=72)	DLCO<50% (n=58)	DLCO≥50% (n=42)
Age, years	-0.39 (<0.001)	-0.37 (0.02)	-0.37 (0.001)	-0.50 (<0.001)	-0.12 (0.46)
Male sex	- (0.52)	- (0.57)	- (0.33)	- (0.46)	- (0.04)
Ever-smoker	- (0.042)	- (0.09)	- (0.46)	- (0.06)	- (0.77)
Pack-years	-0.13 (0.20)	-0.13 (0.44)	-0.05 (0.67)	-0.13 (0.32)	0.17 (0.36)
Body mass index, kg/m²	-0.13 (0.17)	0.04 (0.81)	-0.17 (0.15)	-0.02 (0.86)	-0.39 (0.01)
FVC, %-predicted	0.41 (<0.001)	0.43 (0.006)	0.35 (0.003)	0.11 (0.40)	0.39 (0.01)
DLCO, %-predicted	0.55 (<0.001)	0.64 (<0.001)	0.50 (<0.001)	0.48 (<0.001)	0.18 (0.26)
Depression (HADS)	-0.30 (0.001)	-0.44 (0.005)	-0.21 (0.08)	-0.33 (0.01)	-0.19 (0.22)
Anxiety (HADS)	-0.05 (0.57)	0.04 (0.82)	-0.09 (0.45)	-0.009 (0.95)	-0.14 (0.39)
Sleep quality (PSQI)	-0.15 (0.12)	-0.05 (0.74)	-0.25 (0.03)	-0.008 (0.95)	-0.38 (0.01)
Pain severity (BPI-SF)	-0.22 (0.02)	-0.24 (0.14)	-0.24 (0.04)	-0.31 (0.02)	-0.32 (0.04)
Pain interference (BPI-SF)	-0.29 (0.002)	-0.28 (0.09)	-0.31 (0.008)	-0.33 (0.01)	-0.28 (0.07)
Education, years	0.09 (0.37)	0.19 (0.25)	0.09 (0.44)	-0.004 (0.98)	0.15 (0.34)
Family size	0.16 (0.09)	0.14 (0.40)	0.19 (0.12)	0.12 (0.36)	-0.01 (0.94)
Annual household income	- (0.07)	- (0.67)	- (0.049)	- (0.13)	- (0.07)

Ten patients whose DLCO %-predicted values could not be measured were excluded from the analysis.

Abbreviations: BPI-SF, Brief Pain Inventory short form; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; PSQI, Pittsburgh Sleep Quality Index.

Table 3. Adjusted association of extrapulmonary deficits with daily step count. Each row represents a separate multivariable model that was adjusted for age, sex, pack-years, ILD subtype, FVC %-predicted, DLCO %-predicted, and average temperature and hours of daylight during the one-week period. The adjusted R2 of the baseline model was 0.36 without extrapulmonary deficits.

Variable	Coefficient	*p*-value	Adjusted R^2
Depression	-156	0.10	0.37
Anxiety	28	0.79	0.35
Sleep quality	-131	0.20	0.43
Pain severity	-323	0.09	0.37
Pain interference	-312	0.09	0.37

Table 4. Exploratory stepwise regression model to identify independent predictors of daily step count in patients with fibrotic ILD. Both forward selection and backward elimination approaches produced the same final multivariable model shown in this table.

Variable	Coefficient	*p*-value
Age	-119	0.001
FVC, %-predicted	43	0.03
DLCO, %-predicted	73	0.002
Pain severity	-380	0.03

Adjusted $R^2 = 0.35$, $p<0.001$

Table 5. Baseline physical activity of the study cohort. All values are expressed as median (interquartile range).

Activity parameters	IPAQ-LF	Activity monitors			
		Waist	Waist LFE	Wrist	Wrist LFE
MVPA (*mins/week*)	200 (30-563)	87 (17-225)	113 (35-270)	1,569 (1,074-2,059)	1,692 (1,168-2,160)
EE *(MET-mins/week)*	2,160 (718-4,269)	1,548 (926-3,031)	1,915 (1,210-3,475)	10,153 (7,002-13,320)	10,782 (7,516-14,015)
Sedentary time (*mins/day)*	360 (240-566)	337 (256-418)	294 (219-389)	54 (37-96)	48 (33-93)
Inactive time *(mins/week)*	9,480 (9,048-9,883)	5,770 (5,080-6,622)	5,453 (4,825-6,363)	3,932 (3,510-4,272)	3,917 (3,486-4,265)
Daily steps	-	3,853 (2,236-6,805)	10,389 (7,278-14,608)	7,918 (6,003-10,702)	15,192 (11,552-19,175)

Abbreviations: EE, energy expenditure; IPAQ-LF, International Physical Activity Questionnaire long form; LFE, low frequency extension; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity.

Table 6. Construct validity of the IPAQ-LF. Spearman rank correlations of the IPAQ-LF with corresponding measurements from waist activity monitor without LFE.

IPAQ-LF	**Waist activity monitor without LFE**	
	***r*-value**	***p*-value**
MVPA (*mins/week*)	0.23	0.01
Energy expenditure (*MET-mins/week*)	0.50	<0.001
Sedentary time (*mins/day*)	0.37	<0.001
Inactive time (*mins/week*)	0.39	<0.001

Abbreviations: IPAQ-LF, International Physical Activity Questionnaire long form; LFE, low frequency extension; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity.

Table 7. Criterion validity of the IPAQ-LF. Spearman rank correlations of the IPAQ-LF and activity monitor measurements with relevant clinical outcomes; *p*-values are shown in brackets.

IPAQ-LF				
Clinical parameters	**MVPA**	**Energy expenditure**	**Sedentary time**	**Inactive time**
FVC, %-predicted	0.30 (0.002)	0.28 (0.003)	-0.04 (0.70)	-0.27 (0.004)
DLCO, %-predicted	0.25 (0.01)	0.38 (<0.001)	-0.10 (0.31)	-0.40 (<0.001)
Daily steps*	0.39 (<0.001)	0.55 (<0.001)	-0.37 (<0.001)	-0.53 (<0.001)
EQ-5D index score	0.30 (0.006)	0.38 (<0.001)	-0.31 (0.003)	-0.39 (<0.001)
Waist activity monitor without LFE				
Clinical parameters	**MVPA**	**Energy expenditure**	**Sedentary time**	**Inactive time**
FVC, %-predicted	0.40 (<0.001)	0.40 (<0.001)	-0.27 (0.005)	-0.19 (0.04)
DLCO, %-predicted	0.54 (<0.001)	0.56 (<0.001)	-0.23 (0.02)	-0.25 (0.01)
EQ-5D index score	0.37 (<0.001)	0.34 (0.01)	-0.34 (0.002)	-0.37 (<0.001)

* Daily steps measured from waist activity monitor without LFE

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; EQ-5D, European Quality of Life 5 Dimensions 5-level version; FVC, forced vital capacity; IPAQ-LF, International Physical Activity Questionnaire long form; LFE, low frequency extension; MVPA, moderate-to-vigorous physical activity.

Table 8. Anchor- and distribution-based estimates of MID for MVPA. The measurements from the IPAQ-LF and waist activity monitor were used to estimate the MID.

Anchor-based MID			
	Regression equation for MVPA	**MID for anchor**	**MID for MVPA minutes/week** Midpoint (range)
Activity monitor	-157 + 4.1 × FVC	2 to 6%	**16 (8 to 25)**
	-90 + 5.3 × DLCO	10-14%	**64 (53 to 74)**
	-138 + 381 × EQ-5D	0.037 to 0.069	**20 (14 to 26)**
IPAQ-LF	-105 + 6.6 × FVC	2 to 6%	**26 (13 to 39)**
	239 + 0.03 × Daily steps	600 to 1,100 steps/day	**27 (19 to 35)**
	-285 + 836 × EQ-5D	0.037 to 0.069	**44 (31 to 58)**

Distribution-based MID		
	0.5 SD *(mins/week)*	**1 SEM** *(mins/week)*
Activity monitor	104	69
IPAQ-LF	242	227

Anchor-based MID			
	Regression equation for MVPA	**MID for anchor**	**MID for MVPA minutes/week** Midpoint (range)
Activity monitor	-157 + 4.1 × FVC	2 to 6%	**16 (8 to 25)**
	-90 + 5.3 × DLCO	10-14%	**64 (53 to 74)**
	-138 + 381 × EQ-5D	0.037 to 0.069	**20 (14 to 26)**
IPAQ-LF	-105 + 6.6 × FVC	2 to 6%	**26 (13 to 39)**
	239 + 0.03 × Daily steps	600 to 1,100 steps/day	**27 (19 to 35)**
	-285 + 836 × EQ-5D	0.037 to 0.069	**44 (31 to 58)**

Distribution-based MID		
	0.5 SD *(mins/week)*	**1 SEM** *(mins/week)*
Activity monitor	104	69
IPAQ-LF	242	227

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; EQ-5D, European Quality of Life 5 Dimensions 5-level version index score; FVC, forced vital capacity; IPAQ-LF, International Physical Activity Questionnaire long form; LFE, low frequency extension; MID, minimally important difference; MVPA, moderate-to-vigorous physical activity; SD, standard deviation; SEM, standard error of measurement.

Figures

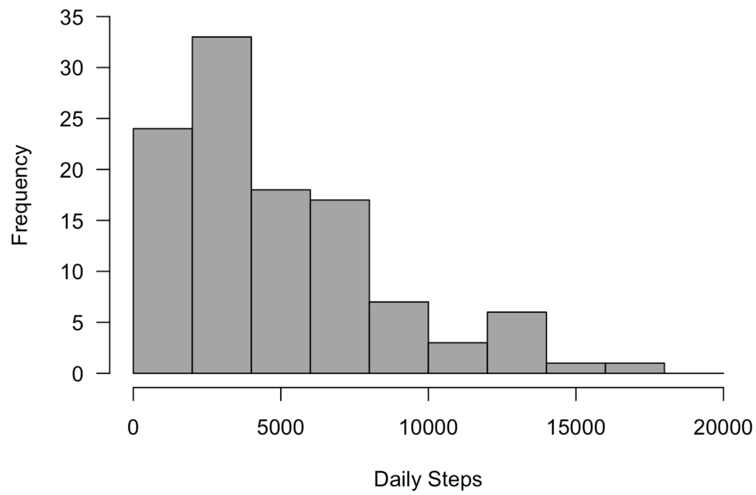

Figure 1. Histogram of daily step counts in patients with fibrotic ILD measured by waist activity monitors.

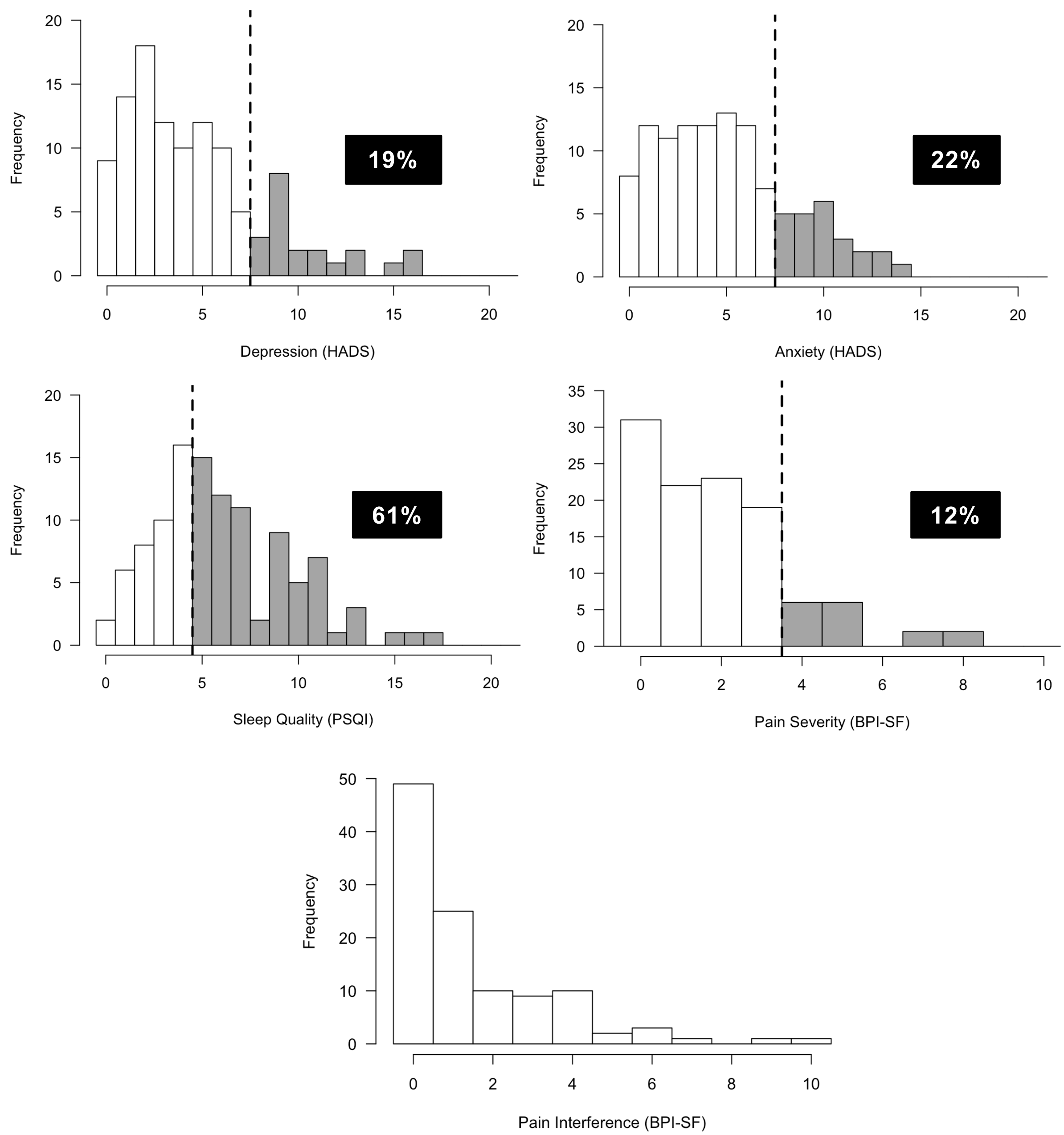

Figure 2. Distribution and prevalence of extrapulmonary deficits in patients with fibrotic ILD. Dashed lines indicate pre-specified clinically meaningful thresholds for each questionnaire, excluding BPI-SF pain interference that does not have an established threshold. Grey and white bars indicate patients with and without clinically meaningful scores for extrapulmonary deficits, respectively.

Abbreviations: BPI-SF, Brief Pain Inventory short form; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index.

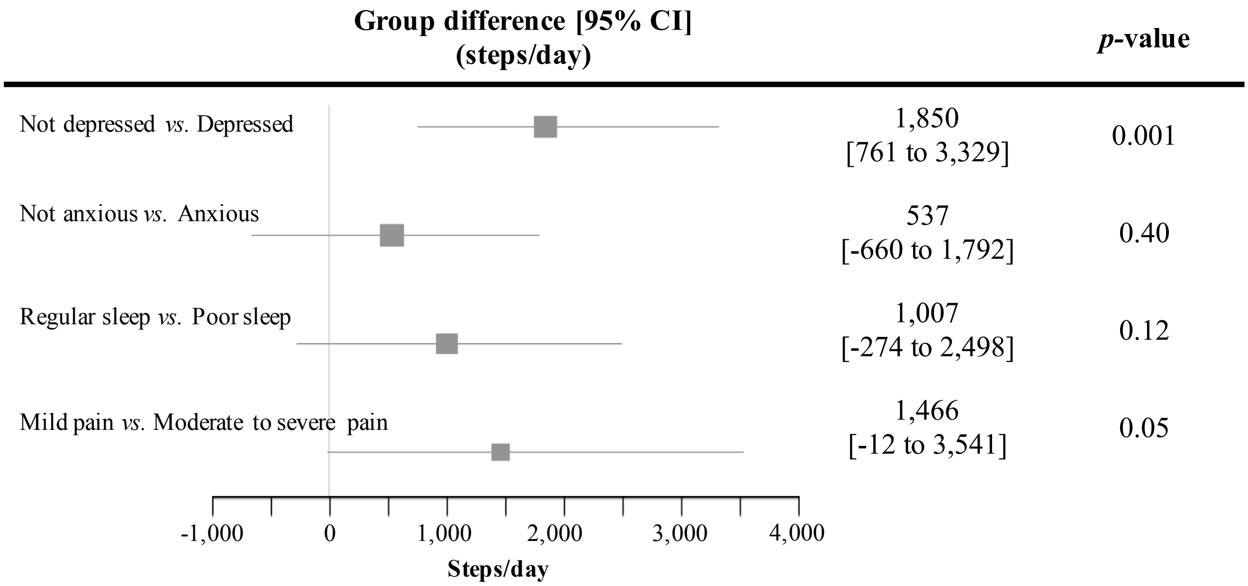

Figure 3. Comparison of daily step counts in patients with and without extrapulmonary deficits. The group difference, 95% confidence intervals, and *p*-values were generated using the non-parametric Wilcoxon rank sum test.

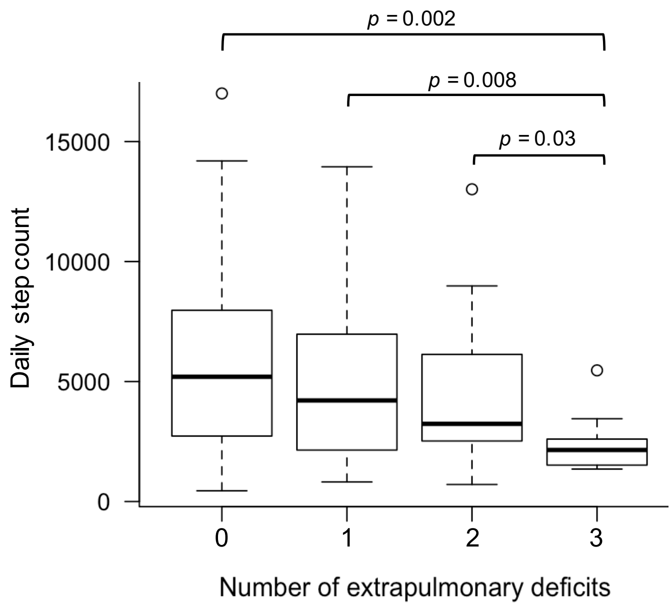

Figure 4. Mean daily step counts of patients with extrapulmonary deficits. Three patients with four extrapulmonary deficits were excluded from this figure given the small number of patients in this group.

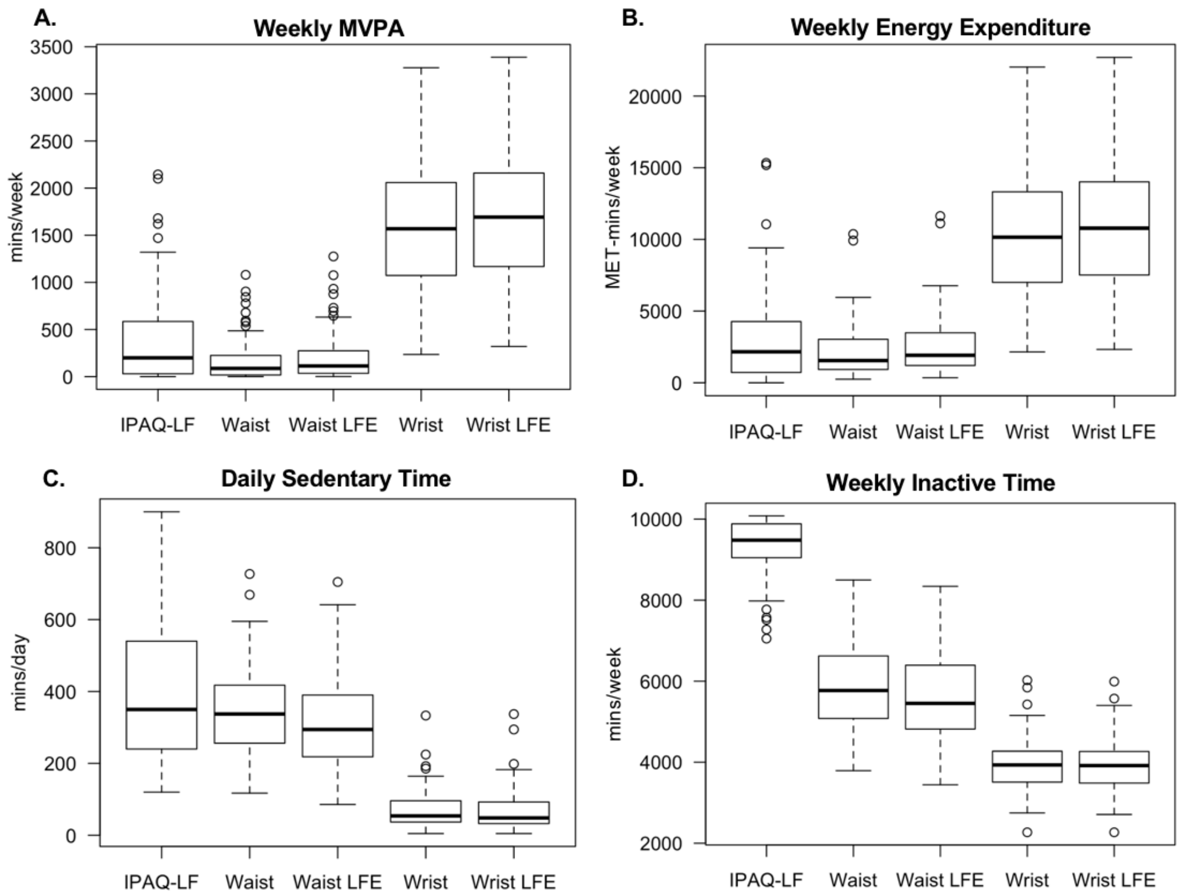

Figure 5. Comparison of self-reported IPAQ-LF physical activity parameters and activity monitors data.

Abbreviations: IPAQ-LF, International Physical Activity Questionnaire long form; LFE, low frequency extension; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity.

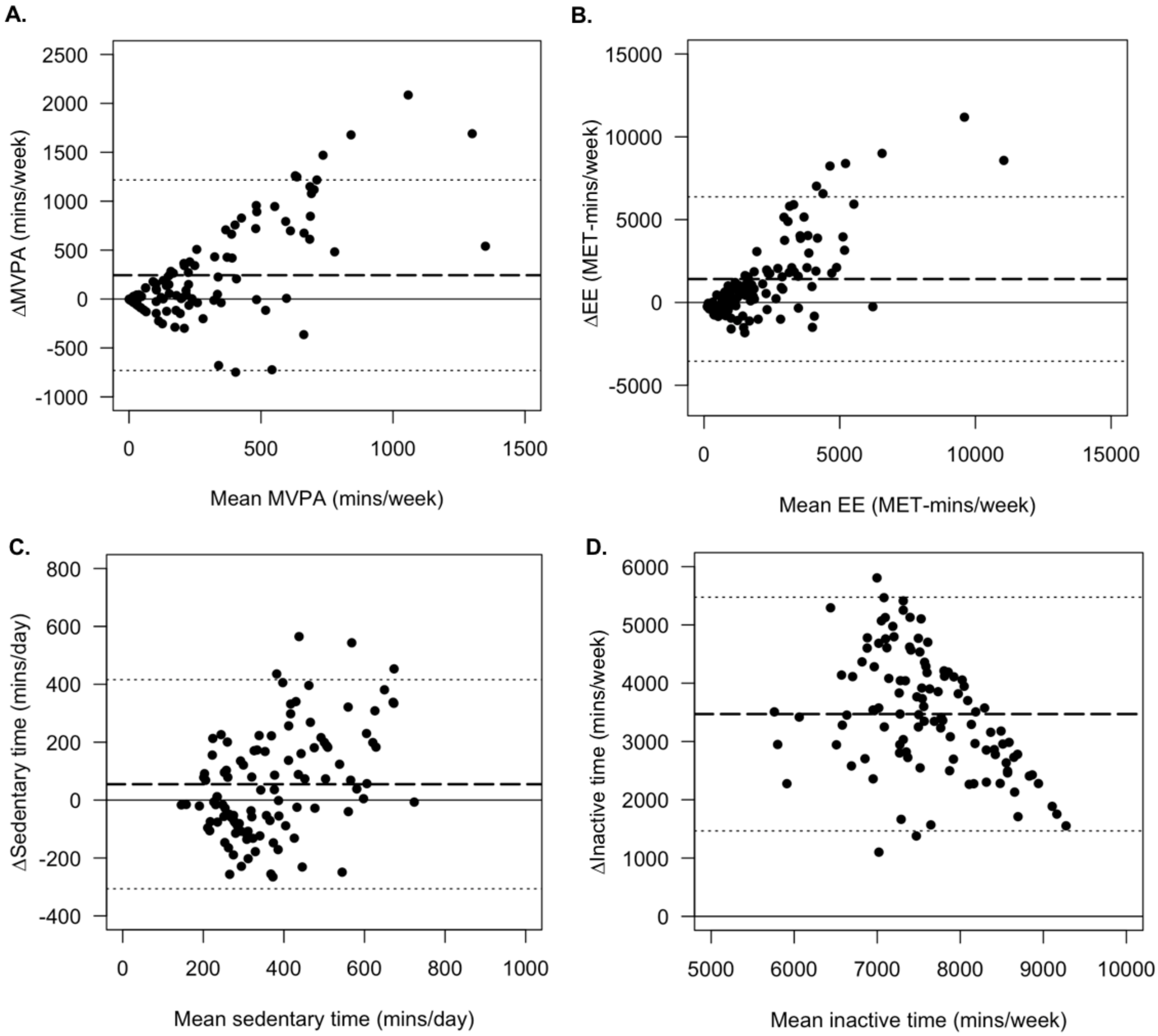

Figure 6. Bland-Altman plots comparing the agreement of IPAQ-LF and waist activity monitor measurements. The difference in measurements (IPAQ-LF estimates minus activity monitor data) is shown in relation to the mean of two measurements. The dashed line indicates the average difference in measurements between IPAQ-LF and activity monitor; the dotted lines represent the limits of agreement, defined as 1.96 standard deviations of the difference in measurements.

Abbreviations: EE, energy expenditure; MET, metabolic equivalent of task; mins, minutes; MVPA, moderate-to-vigorous physical activity.

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Appendices

Appendix A. Sample size calculation. List of hypothetical R^2 values used to calculate sample size needed for 80-90% power. The rows highlighted in red represent worst-case scenarios, whereas the rows highlighted in green indicates our anticipated results.

Baseline R^2	ΔR^2 with extrapulmonary deficits	Total R^2	Power	Sample size
0.2	0.1	0.3	0.80	89
0.2	0.2	0.4	0.80	42
0.3	0.1	0.4	0.90	98
0.3	0.2	0.5	0.90	45
0.4	0.1	0.5	0.90	83
0.4	0.2	0.6	0.90	37
0.5	0.1	0.6	0.90	67
0.5	0.2	0.7	0.90	30

Appendix B. Comparison of physical activity in patients with IPF and non-IPF ILDs. Physical activity is reported as median (interquartile range). *p*-values represent the statistical significance of the difference between the two groups for each variable, as determined by the non-parametric Wilcoxon rank sum test.

Physical activity parameters	IPAQ-LF	Waist activity monitor without LFE
MVPA (*mins/week*)		
IPF	130 (0-405)	69 (23-205)
Non-IPF	225 (75-593)	103 (16-225)
p-value	0.05	0.78
Energy expenditure (*MET-mins/week*)		
IPF	1,805 (309-3,997)	1,500 (1,063-2,573)
Non-IPF	2,314 (1,022-4,842)	1,580 (926-3,058)
p-value	0.14	0.62
Sedentary time (*mins/day)*		
IPF	386 (244-600)	387 (284-492)
Non-IPF	330 (240-531)	318 (240-400)
p-value	0.23	0.008
Inactive time (*mins/week*)		
IPF	9,660 (9,150-10,015)	6,005 (5,230-7,034)
Non-IPF	9,468 (8,813-9,821)	5,690 (4,931-6,438)
p-value	0.12	0.05
Daily steps		
IPF	-	3,451 (1,622-6,505)
Non-IPF		4,202 (2,693-6,805)
p-value		0.19

Abbreviations: IPAQ-LF, International Physical Activity Questionnaire long form; LFE, low frequency extension; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity.

Appendix C. Self-reported physical activity of patients with fibrotic ILD as measured by the IPAQ-LF.

IPAQ-LF domains	Minutes/week		MET-minutes/week	
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)
Work-related				
Walking	37±135	0 (0-0)	122±445	0 (0-0)
Moderate	38±149	0 (0-0)	150±598	0 (0-0)
Vigorous	20±120	0 (0-0)	163±961	0 (0-0)
Total	**95±341**	**0 (0-0)**	**435±1,676**	**0 (0-0)**
Transportation-related				
Walking	188±227	120 (0-300)	620±749	396 (0-990)
Cycling†	3±15	0 (0-0)	15±89	0 (0-0)
Total	**190±228**	**120 (0-300)**	**634±759**	**396 (0-990)**
Housework-related				
Moderate (inside)	184±315	60 (0-240)	551±945	180 (0-720)
Moderate (outside)	99±211	0 (0-95)	395±846	0 (0-380)
Vigorous†	28±89	0 (0-0)	155±491	0 (0-0)
Total	**310±414**	**179 (0-420)**	**1,100±1,468**	**540 (0-1,500)**
Leisure time				
Walking	119±203	20 (0-140)	393±671	66 (0-462)
Moderate	44±112	0 (0-30)	176±447	0 (0-120)
Vigorous	28±83	0 (0-0)	225±662	0 (0-0)
Total	**191±278**	**70 (0-345)**	**793±1,176**	**259 (0-1,230)**
Sitting time				
Weekday	401±198*	360 (240-600)	-	-
Weekend	394±198*	330 (240-540)	-	-
Average	**396±194***	**360 (240-566)**	-	-
Weekly total				
Walking	**342±379**	**195 (60-490)**	**1,135±1,247**	**644 (198-1,617)**
Moderate	**350±433**	**180 (20-495)**	**1,441±1,674**	**780 (130-2,226)**
Vigorous	**49±153**	**0 (0-0)**	**387±1,222**	**0 (0-0)**
Total	**741±692**	**600 (198-1,033)**	**2,963±2,938**	**2,160 (718-4,269)**

* Sitting time is reported as minutes/day

† As previously described,[11] cycling and vigorous housework-related activity were categorized as moderately intense when calculating total weekly physical activity minutes.

Abbreviations: IPAQ-LF, International Physical Activity Questionnaire long form; IQR, interquartile range; MET, metabolic equivalent of task; SD, standard deviation.

Appendix D. Subgroup analysis of MID for MVPA using the anchor-based method.

ANCHOR-BASED MID			
	Regression equation for MVPA	**MID for anchor**	**MID for MVPA minutes/week** Midpoint (range)
IPF			
Activity monitor	-290 + 6.1 × FVC	2 to 6%	**24 (12 to 36)**
	-151+ 7.2 × DLCO	10-14%	**86 (72 to 101)**
	-636 + 998 × EQ-5D	0.037 to 0.069	**53 (37 to 69)**
IPAQ-LF	-367 + 9.0 × FVC	2 to 6%	**36 (18 to 54)**
	50 + 0.06 × Daily steps	600 to 1,100 steps/day	**48 (34 to 62)**
	25 + 344 × EQ-5D	0.037 to 0.069	**18 (13 to 24)**
Non-IPF			
Activity monitor	-103 + 3.3 × FVC	2 to 6%	**13 (7 to 20)**
	-71 + 4.6 × DLCO	10-14%	**55 (46 to 64)**
	-43 + 253 × EQ-5D	0.037 to 0.069	**13 (9 to 17)**
IPAQ-LF	60 + 4.9 × FVC	2 to 6%	**20 (10 to 29)**
	372 + 0.01 × Daily steps	600 to 1,100 steps/day	**12 (8 to 15)**
	-333 + 947 × EQ-5D	0.037 to 0.069	**50 (35 to 65)**

DISTRIBUTION-BASED MID		
	0.5 SD *(mins/week)*	**1 SEM** *(mins/week)*
IPF		
Activity monitor	**127**	**84**
IPAQ-LF	**204**	**192**
Non-IPF		
Activity monitor	**91**	**60**
IPAQ-LF	**258**	**242**

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; EQ-5D, European Quality of Life 5 Dimensions 5-level version index score; FVC, forced vital capacity; IPAQ-LF, International Physical Activity Questionnaire long form; IPF, idiopathic pulmonary fibrosis; MID, minimally important difference; MVPA, moderate-to-vigorous physical activity.