



UNIVERSITY OF  
BIRMINGHAM

**PHYSICAL ACTIVITY, EXERCISE, AND SEDENTARY  
BEHAVIOUR ON FATIGUE IN RHEUMATOID ARTHRITIS**

**By**

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## **ABSTRACT**

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune joint disease characterised by chronic high-grade systemic inflammation. Individuals with RA experience symptoms like fatigue, pain, inflammation, and joint stiffness, along with wellbeing and psychological challenges that affect their general quality of life. People with RA often have relatively low levels of physical activity (PA) and have relatively high levels of sedentary behaviour (SB).

This aim of this thesis was to explore the associations between PA, exercise, and SB with fatigue in people with RA using different methodological approaches. The thesis includes a review which examined these associations (**Chapter 2**). A novel aspect of this work was the inclusion of observational, longitudinal, and intervention studies in the same review to get a detailed understanding of the existing literature. The findings from the review showed that observational studies provided more substantial evidence for associations between PA and fatigue, whereas exercise interventions appeared to be more effective in reducing fatigue. Few studies explored the associations between SB and fatigue in RA. The review also found a lack of consistency of measuring fatigue in these studies, with some using validated multidimensional measures of fatigue, whereas others included a unidimensional fatigue measure.

In the subsequent chapters, different methods and assessments were used to measure fatigue. **Chapter 3** examined the diurnal variation in PA and SB and its associations with a multidimensional measure of fatigue. The findings indicated that people with RA tend to be more sedentary and less physically active in the evening compared to the morning and afternoon. In addition, sedentary time,

standing and stepping are differentially associated with dimensions of fatigue in RA, with stepping behaviours (time and intensity) demonstrating the most consistent associations across all fatigue dimensions.

**Chapter 4** used both a multidimensional measure of fatigue as well as unidimensional assessment which was recorded throughout the day for 1 week to provide an overall measure of fatigue in university students, as well as a device-based measures of PA and SB. It was found that daily PA and sedentary time were not associated with multidimensional aspects of fatigue in this population. Using ecological momentary assessment (EMA) was a suitable method to capture unidimensional fatigue over the course of a week. However, these measures were not associated with PA or sedentary time in this population.

The combined findings of this thesis indicate a plausible role of increasing PA (including exercise) for managing fatigue in RA. However, limited evidence exists for the role of sedentary time. In all cases, more research is required to uncover the complexities of the associations between these movement behaviours and fatigue in RA, particularly when considering the complex and multidimensional nature of the experience of fatigue. EMA-methods employing multidimensional measures of fatigue, alongside device-based assessments of PA and sedentary time, may show some promise, but further development and validation work of fatigue measurement is required prior to implementing such studies in RA.

***I would like to dedicate this thesis to my mum and family***

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## List of abbreviations

<b>ADLs</b>	Activities of Daily Living
<b>AM</b>	Morning
<b>BDMARDs</b>	Biologic Disease Modifying Antirheumatic Drugs
<b>BRAF MDQ</b>	Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire
<b>CFS</b>	Chronic Fatigue Syndrome
<b>CG</b>	Control Group
<b>CIS-20</b>	Checklist of Individual Strengths -20
<b>CRF</b>	Cardiorespiratory Fitness
<b>CVD</b>	Cardiovascular Disease
<b>DAS28</b>	Disease Activity Score-28
<b>DMARDs</b>	Disease Modifying Antirheumatic Drugs
<b>EMA</b>	Ecological Momentary Assessment
<b>EU</b>	European Union
<b>EULAR</b>	European Alliance Associations for Rheumatology
<b>Exe</b>	Exercise
<b>FACIT</b>	Functional Assessment of Chronic Illness Therapy fatigue scale
<b>Freq</b>	Frequency
<b>HAQ</b>	Stanford Health Assessment
<b>HEPA</b>	Health-Enhancing Physical Activity
<b>HR</b>	Heart Rate
<b>IG</b>	Intervention Group
<b>Int</b>	Intensity
<b>IPAQ</b>	International Physical Activity Questionnaire
<b>LPA</b>	Light Physical Activity
<b>MAF</b>	Multi-Dimensional Assessment of Fatigue
<b>MET</b>	Metabolic Equivalent of Task
<b>MFI</b>	Multi-Dimensional Fatigue Inventory
<b>MS</b>	Multiple Sclerosis
<b>MVPA</b>	Moderate – Vigorous Physical Activity

<b>NRS</b>	Numerical Rating Scales
<b>NSAIDs</b>	Non-Steroidal Anti- Inflammatory Drugs
<b>OMERACT</b>	Outcomes Measures in Rheumatoid Arthritis Clinical Trials
<b>OR</b>	Osteoarthritis
<b>PA</b>	Physical Activity
<b>PAEI</b>	Paffenbarger Physical Activity and Exercise Index
<b>PAS2</b>	Physical Activity Scale
<b>PD</b>	Programme Duration
<b>PM 1</b>	Afternoon
<b>PM 2</b>	Evening
<b>POMS</b>	Profile of Moods Scale
<b>POMS-F</b>	Profile of Mood States-Fatigue
<b>PRISMA</b>	Preferred Reporting Items for Systematic reviews and Meta-Analyses
<b>PROMIS</b>	Patient-Reported Outcome Measurement Information System
<b>QUEST-RA</b>	Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis
<b>RA</b>	Rheumatoid Arthritis
<b>RCT</b>	Randomised Controlled Trial
<b>SB</b>	Sedentary Behaviour
<b>SD</b>	Standard Deviation
<b>SQUASH</b>	Short Questionnaire to Assess Health-enhancing physical activity
<b>ST</b>	Sedentary Time
<b>TNF</b>	Tumor Necrosis Factor
<b>UK</b>	United Kingdom
<b>US</b>	United States
<b>USA</b>	United States of America
<b>VAS</b>	Visual Analogue Scales
<b>β</b>	Standardised Beta Coefficient

## **CHAPTER 1**

### **CHAPTER 1: GENERAL INTRODUCTION**

## Definition and symptoms of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease that impacts the joints characterised by persistent inflammation, joint damage, and changes, in joint shape ([Sharif et al., 2018](#)). It is known for causing polyarthritis in small joints, but with potential extra-articular manifestations as well ([Gulati et al., 2018](#)).

RA commonly presents with symptoms such as pain, swelling and stiffness in the joints ([Sparks, 2019](#)). These manifestations can be accompanied by redness. The condition may also result in an accumulation of fluid, inflammation of the membrane and fragile cartilage all contributing to joint discomfort and rigidity ([Carson-DeWitt, 2011](#)). The intensity of these symptoms can vary, with morning stiffness serving as a feature indicating disease activity ([Sierakowski and Cutolo, 2011](#)). Together, these symptoms can impact on physical function and overall quality of life ([Sparks, 2019](#)). In the early stages of RA, joints may not be affected. RA can also manifest in just one joint or a few joints showing different types of joint involvement ([Halla et al., 2004](#)). The joints that are commonly impacted include the hands ( proximal interphalangeal joints) and feet (metatarsophalangeal joints) with the wrists often being affected as well ([Emery, 2011](#); [Ucar, 2014](#)). Given that the disease is chronic, it is possible that over the course of time, limited movement and decreased mobility becomes more evident. Research indicates that 17% of individuals show no signs of impairment a decade after being diagnosed with RA ([Lindqvist, 2003](#)). Joint deterioration a process, in the two decades of RA contributes to around a quarter of the disability seen in long standing RA cases ([Scott et al., 2003](#)). This

highlights the importance of starting treatment and taking measures to slow down the advancement of the disease (Aletaha and Smolen, 2018). It is worth important to emphasise that RA does not only affects the joints, but it can also have an impact on psychological wellbeing. For example, depression and anxiety are more common in people with RA compared to the general population (Nicolau et al., 2023). Fatigue is also a prominent symptom of RA. As this is a main topic of this thesis more detailed information about fatigue in RA will be presented later.

RA is linked to health conditions, such, as high blood pressure, osteoporosis, CVD, lung diseases and mood disorders (Kłodziński and Wisłowska, 2018; Taylor et al., 2021). Additionally certain health conditions, like bowel disease, type 1 diabetes and venous thromboembolism could increase the risk of developing RA. On the other hand, conditions such as sleep apnea and venous thromboembolism may arise following an RA diagnosis (Kronzer et al., 2019). The occurrence of health issues, including mental wellbeing and circulatory diseases alongside RA is quite common (Hill et al., 2022). These additional health conditions could affect how well patients respond to treatments (Taylor et al., 2021). They can also influence how often healthcare services are used medical costs incurred and even the survival rates of individuals with RA (Han and Han, 2016).

### **Prevalence of Rheumatoid Arthritis**

RA is a condition that affects people worldwide with reported prevalence rates in adults ranging from 0.4% to 1.3% (Akkoc, 2008; Almutairi et al., 2021).

Research conducted in North American countries suggests that the prevalence

ranges from 0.5% to 1.1% with annual occurrences varying between 100,000 cases, per 20 to 50 individuals ([Alamanos et al., 2005](#)). In the United Kingdom, the prevalence rates are 1.16% for men and 1.44% for women. It is worth noting that older individuals and women are more commonly affected by this condition compared to men ([Iikuni et al., 2009](#); [Shaul, 1994](#)). RA has been reported to be 3 times as more frequent in women compared to men ([Favalli et al., 2019](#)).

### **Treatment of Rheumatoid Arthritis**

Advancements in the pharmaceutical industry have led to improved treatments for RA. A variety of medications are now commonly prescribed for the treatment of RA. While traditional approaches, like plasma exchange and immunotherapy have been studied in the past, their effectiveness is still being investigated ([Shiokawa, 1983](#)). Disease modifying antirheumatic drugs (DMARDs) such as methotrexate, hydroxychloroquine and leflunomide are currently utilised as first line treatment to target molecules involved in immune and inflammatory responses ([Abbasi et al., 2018](#); [Roberts et al., 2004](#)). Where patients do not respond to DMARDs, they are escalated to receive more intensive, biologic therapies, such as tumor necrosis factor (TNF) blocking medications. A meta-analysis conducted by Alonso Ruiz revealed that anti-TNF $\alpha$  medication such as infliximab, etanercept and adalimumab demonstrate effectiveness and safety in treating RA ([Alonso-Ruiz et al., 2008](#)). In addition to DMARDs and/or biologic therapies, more non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are used to relieve pain and inflammation.

More recently, there has been a focus on incorporating non-pharmacological interventions alongside pharmacological treatment of RA, to manage symptoms

and support control of disease activity. These non-pharmacological approaches involve increasing engagement in physical activity and exercise, which has proven effective in alleviating RA symptoms and reducing systemic manifestations, as well as reducing co-morbidities in RA ([Metsios and Kitas, 2018](#)).

Over the last decade, nonpharmacological interventions focussed on supporting physical activity have received increased attention for supporting self-management of RA. The European Alliance Associations for Rheumatology (EULAR) has consistently emphasised the importance of engaging in PA as a part of RA treatment ([Osthoff et al., 2018](#)). Despite these suggestions many individuals with RA tend to lead more sedentary lifestyles ([Schouller et al., 2019](#)). Therefore, following EULARs guidance on PA is essential, for enhancing the health and quality of life of RA patients ([Gwinnutt et al., 2022](#)). This thesis will specifically focus on physical activity, sedentary behaviour, and fatigue. Therefore, the next sections will provide a more detailed report on these different aspects.

### **Fatigue in Rheumatoid Arthritis**

Fatigue is a debilitating symptoms experienced by individuals with RA ([Pope, 2020](#); [Silva et al., 2020](#)). As a result, the RA community widely recognise fatigue as a key concern impacting overall quality of life of people living with RA ([Hewlett et al., 2005](#)). In 2007 international consensus was reached by the Outcomes Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) project to include fatigue in the "core set" of outcome measurements for all studies ([Kirwan et al., 2007](#)), and therefore emphasising the significance of fatigue in

RA. Studies have shown that severe fatigue in RA is associated with factors such as pain, functioning and psychosocial aspects than inflammation alone ([Van Hoogmoed et al., 2010](#)). Addressing fatigue in RA treatment therefore requires a more in-depth analysis of factors which may provide insights into patterns of fatigue, as well as physical and psychosocial factors that may impact its occurrence and intensity ([Dupond, 2011](#)).

### **Definition, prevalence, and impact of fatigue**

Fatigue is a feeling of weakness, reduced energy, overall tiredness, or a sense of exhaustion ([Mayoux-Benhamou, 2006](#)). Fatigue is a common problem among adults with RA. Some studies report prevalence rates of over 80%.

Furthermore, the fatigue is more severe in RA patients compared to healthy controls ([Belza, 1995](#)). While others suggest that 40% of RA patients may experience severe fatigue like those with chronic fatigue syndrome (CFS) ([Repping-Wuts et al., 2007](#)). Fatigue is a prevalent and significant symptom in RA patients in the UK, with up to 70% experiencing it ([Hewlett, Chalder, et al., 2011](#)). This is consistent with the global prevalence of severe fatigue in RA, which ranges from 41% to 57% ([Overman et al., 2016](#)).

The high prevalence of fatigue has led to researchers studying the impact of this symptom on the quality of life and wellbeing of this patient group. Various studies have shown how fatigue is linked to the risk of work disability and unemployment among RA patients playing a role in determining their socioeconomic status ([Dadoniene et al., 2004](#); [Gron et al., 2014](#); [Wolfe et al., 1996](#)). Apart from its influence on work ability fatigue affects areas of daily life for those dealing with RA. Research indicates that fatigue reduces productivity

and contributes to rates of unemployment among affected individuals highlighting its societal implications (Sokka, 2003). Additionally, studies highlight fatigue as an indicator of long-term work disability in RA management underscoring its importance for predicting outcomes (Van Amelsvoort et al., 2002). Given the effects of RA related fatigue it is essential to manage it to enhance the quality of life for patients. Experts stress the need for approaches that address not the physical symptoms but also the psychological and social impacts of fatigue (Mayoux-Benhamou, 2006). By taking a strategy, towards addressing fatigue in healthcare medical professionals can provide improved assistance to individuals with RA in managing the difficulties associated with this symptom.

### **What causes fatigue?**

The feeling of fatigue in RA is intricate and diverse, and greatly influences the lives of individuals. Comprehending the mechanisms and causal relationships of fatigue in RA is challenging due to its multifaceted nature. It is suggested that interactions occur among factors such as the RA disease process (inflammation, pain, disability, muscle strength and deconditioning), thoughts, emotions, behaviours (beliefs about illness, anxiety, depression) and personal life aspects (work situation, health status, support network) (Katz et al., 2016). Indeed, research has shown fatigue to be influenced by a combination of factors including; inflammation, pain, mood, personality traits, sleep patterns, obesity, and other medical conditions (Pope, 2020). Other general factors such as obesity, physical inactivity and depression also contribute significantly to fatigue (Katz, 2017). The experience of fatigue in RA also differs based on age and gender with its root causes still not fully grasped (Nikolaus, 2012). Despite

these discoveries the exact origins of fatigue in RA remain uncertain. In addition, the above research demonstrating the number of factors that may be linked to the occurrence of fatigue in RA, highlight the multidimensional nature of fatigue, which poses challenges for both its assessment and management ([Santos, Duarte, da Silva, et al., 2019](#)). Further studies are therefore crucial for pinpointing sources of fatigue, which may shed light on effective avenues for fatigue management ([Katz, 2017](#)).

### **Fatigue Assessment**

Measuring fatigue often involves using self-report questionnaires or scales ([Hewlett et al., 2007](#)). These tools usually prompt individuals to assess their fatigue levels considering factors, like how severe the fatigue is, how often it occurs, and how it affects their routines. Yet, there is no agreement on the suitable questionnaire or scale to employ resulting in differences in evaluation methods across research studies and medical environments ([Beckers et al., 2023](#)). Currently, ways to assess fatigue are categorised into two main types of assessment tools: unidimensional or multidimensional. Unidimensional methods for evaluating fatigue tend to concentrate on gauging fatigue according to its level of intensity or seriousness ([Oude Voshaar et al., 2015](#)). Using unidimensional methods, fatigue can be measured using several standardised questionnaires, but it is more easily measured using tools such as visual analogue scales (VAS) and numerical rating scales (NRS). Such methods offer a viewpoint on fatigue but neglect the aspects and complexities of fatigue that different individuals may encounter. It is worth questioning how useful unidimensional measures are because people who report the same fatigue

intensity score, could have different experiences that have resulted in the same level of fatigue. For instance, one individual may experience exhaustion, but maintain mental alertness, while another might feel mentally fatigued but physically well. One-dimensional tools therefore do not give a comprehensive and useful picture of **how** patients experience fatigue, just **how much** they experience fatigue. As such, relying solely on one-dimensional tools prevents us from capturing the complex experience of fatigue in RA patients. Indeed, the constraints of existing unidimensional fatigue assessments underscore the necessity for instruments tailored to RA patients that capture fatigue and its effects on individuals daily experiences (Hewlett, Dures, et al., 2011) . On other hand, multidimensional questionnaire assess the different aspects of fatigue and can provide a greater insight into how individuals experience fatigue. That is, the physical, mental, and emotional aspects of fatigue and how it affects daily life (Nikolaus et al., 2012).

Different questionnaires are available that capture the multidimensional nature of fatigue and offer a more comprehensive insight into fatigue encounters, and have been validated for people with RA. Examples of multidimensional methods include the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAFF MDQ) (Choy and Dures, 2019), Multidimensional Assessment of Fatigue (Hewlett et al., 2007) and Multidimensional Fatigue Inventory (MFI) (Goodchild et al., 2008). The work presented in this thesis will focus on the Multidimensional Fatigue Inventory 20 (MFI 20) (Smets et al., 1995). This questionnaire measures general fatigue (reflecting overall sense of fatigue), physical fatigue (physical sensations of fatigue), mental fatigue (mental sensations, such as cognitive fog or mental drain), as well as reduced activity

(impact of fatigue on doing usual activities or tasks) and reduced motivation (lower willingness to do activities). Therefore, it impacts not just sensations of fatigue, but also the impact of fatigue being able to do or be motivated to do daily activities. This questionnaire has been frequently used in people with RA, including in interventions aiming to impact fatigue in RA ([Farisogullari et al., 2023](#); [Rupp et al., 2004](#); [Santos et al., 2023](#)). In the context of PA and RA, the MFI has revealed some interesting findings, showing the relevance of the different aspects of fatigue. For example, a cross-sectional study found that individuals with RA engaging in regular physical activity reported lower mental fatigue, physical fatigue, general fatigue, as well as less reduced activity ([Løppenthin et al., 2015](#)). Another study reported that mental fatigue was associated with light-intensity PA, whereas physical fatigue was associated with walking, and both physical and mental fatigue were related to exercise ([Brady et al., 2021](#)). These variations in associations between PA and different aspects of fatigue has also been reported in other musculoskeletal conditions. For example, individuals with knee osteoarthritis engaging in light-intensity PA reported lower physical and general fatigue, but no associations were observed with mental fatigue ([Fawole et al., 2020](#)).

Similarly, different aspects of fatigue have been related to sedentary behaviour. For example, two studies reported significantly positive associations between physical fatigue and overall self-reported daily sedentary time in RA ([Brady et al., 2021](#)). Conversely two research studies found positive associations between sedentary time and physical fatigue in individuals with fibromyalgia ([Segura-Jiménez et al., 2017](#)) and rheumatoid arthritis ([O'Brien et al., 2021](#)). An intervention study aimed at reducing sedentary time in RA reported decreases

in activPAL-assessed sedentary time in the intervention group, as well as reductions in all dimensions of fatigue (general, physical, mental, reduced activity, and reduced motivation) (Thomsen et al., 2017). Taken together, there is evidence that PA and sedentary behaviour are associated with different aspects of fatigue, but to get a better understanding of these associations, it is important to use a multidimensional measure of fatigue.

### **Measurement of fatigue in RA**

Various self-reporting tools have been employed to measure fatigue in individuals with RA. In 2007, Hewlett et al conducted a review of fatigue measures in RA and reported that 23 scales were used in research (Hewlett et al., 2007). They reported that only 6 of these scales (including both unidimensional and multidimensional assessment tools) demonstrated adequate validity for measurements of fatigue in RA. The absence of uniformity in fatigue assessment poses a challenge in RA research, creating hurdles in comparing findings across studies, or setting standards for evaluating fatigue in RA. Moreover, cultural and language disparities could add complexity to understanding outcomes from self-reported evaluations. In fact, assessing fatigue in RA is a matter without a consensus,

**The Multidimensional Fatigue Inventory (MFI)** is used to comprehensively assess the multidimensional aspects of fatigue and is frequently used in RA (Rupp et al., 2004). The MFI-20 comprises 20-items which aim to capture different dimensions of fatigue, specifically; general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation (Smets et al., 1995). General fatigue aims to indicate an individual's general a sense of exhaustion,

physical fatigue aims to capture feelings of bodily exhaustion, and mental fatigue considers cognitive aspects like feeling mentally foggy or exhausted. The MFI-20 also considers reduced activity (how much fatigue affects activities or tasks) and reduced motivation (a decrease, in willingness to engage in activities). By incorporating these aspects, the MFI 20 offers a nuanced assessment of fatigue and sheds light on the impacts of fatigue on different aspects of individuals daily lives. Studies have shown the MFI to exhibit high reliability and validity ([Smets et al., 1995](#)), including in people living with RA ([Brady et al., 2021](#)). The MFI may therefore offer a useful measure to assess fatigue from a multidimensional perspective in RA, and if used consistently, could provide some consensus about the causes and consequence of fatigue in RA, to inform fatigue management. However, the extent to which the MFI is currently used is not known. This will be explored in **Chapter 2** of this thesis.

### **Fatigue management**

In the context of RA, fatigue is a debilitating symptom, but research suggests that it is often disregarded by healthcare professionals ([Hewlett et al., 2005](#)), which greatly affects their activities and self-care approaches ([Hewlett et al., 2005](#)). Despite its importance fatigue remains somewhat ambiguous. Patients perceive fatigue differently while clinicians have not given it attention ([Sharpe and Wilks, 2002](#)). This disparity can create difficulties in the doctor patient relationship. The management of fatigue is made complex by its connection to physical, emotional, and social issues ([Ho and Zheng, 2022](#)). Despite these obstacles it is essential for healthcare providers to acknowledge the importance

of fatigue and its influence, on patients' wellbeing, quality of life and strive towards effective treatment approaches.

Treatment approaches may comprise a combination of pharmacological and non-pharmacological intervention. A recent review on pharmacological treatment to manage fatigue in inflammatory rheumatic and musculoskeletal disease (including RA) revealed that pharmacological treatment was effective in reducing fatigue in people with RA. In addition, Especially biologic Disease Modifying Antirheumatic Drugs (bDMARDs) appeared to result in reductions in fatigue ([Farisogullari et al., 2023](#)). These findings indicate that controlling inflammation and disease activity more generally, also helps alleviate fatigue symptoms. Concerning non-pharmacological interventions physical activity and psychosocial treatments have displayed potential in reducing fatigue and enhancing the quality of life for individuals with RA ([Cramp, 2019](#); [Neill et al., 2006](#); [Santos et al., 2023](#)). It is therefore not surprising that engagement in regular physical activity and exercise has been recommended as part of the overall multidisciplinary management of RA patients. For example, the European Alliance of Associations for Rheumatology (EULAR) recommends physical activity as part of the standard of care for patients with RA ([Gwinnutt et al., 2022](#)). In addition, The 2023 EULAR guidelines, for addressing fatigue in individuals with inflammatory rheumatic and musculoskeletal diseases such as RA stress the importance of personalised interventions PA, which are based on the needs and preferences of people with RA, including disease activity and contextual ([Dures et al., 2023](#)).

## Physical activity and sedentary behaviour

Physical activity (PA) involves any movement that uses the body's muscles and requires energy expenditure (Caspersen et al., 1985). PA encompasses a variety of activities both structured and unstructured. Exercise is a sub-set of PA, that refers to organised and repetitive bodily movements, with the aim of improving or maintaining fitness, physical performance, or overall health (Cooney et al., 2011). It is typically categorised as light, moderate or vigorous based on how much effort or energy an individual puts into it. According to the PA guidelines from the US Department of Health and Human Services engaging regularly in moderate to vigorous PA enhances health and lowers the risk of illness and death (Health and Services, 2008). Nevertheless, individuals dealing with illnesses or physical limitations may find it challenging to engage in activities of moderate to vigorous intensity. There is evidence supporting the impact of PA and exercise on individuals, with RA including benefits like better joint health enhanced physical function, increased mobility improved psychological wellbeing and reduced fatigue. Various studies (Cramp, 2019; Cramp et al., 2013; Katz et al., 2018; Neill et al., 2006) have highlighted these advantages. It comes as no surprise that regular PA and exercise are recommended as components in the management of RA patients. Notably organisations like EULAR advocate for incorporating PA into the care for individuals with RA (Gwinnutt et al., 2022). In times medical professionals were hesitant to suggest exercise to individuals with RA due to concerns that it might exacerbate their condition. It was believed that exercise could potentially cause harm (Metsios and Kitas, 2018). There is ample evidence to show that exercise can have impacts for people with RA, including help alleviating pain, decreasing

fatigue, and enhancing overall mobility ([Lee et al., 2006](#); [Nurul and Widiyanto, 2021](#)).

On the other end of the activity continuum is sedentary behaviour. Sedentary behaviour (SB) refers to activities performed while sitting or lying down that have an energy expenditure of  $\leq 1.5$  METs. Typically ranging from 1.0 1.5 METs sedentary behaviour includes actions like watching TV or using a computer ([Bames et al., 2012](#); [Fenton, Veldhuijzen van Zanten, et al., 2018](#)).

Measuring PA and SB in patients with RA has been acknowledged to be complex ([Steultjens et al., 2023](#)). PA and SB can be assessed using either self-report (e.g. questionnaires, diaries) or device-based methods (e.g. accelerometers and pedometers). Many researchers prefer the use of self-report measures for assessing PA and SB because these methods are convenient and cost effective. Examples of commonly used self-report methods include the International Physical Activity Questionnaire (IPAQ), and the Physical Activity Scale (PAS 2) ([Craig et al., 2003](#)). However, device-based approaches (such as accelerometers) provide more objective measurements of PA and SB, enabling continuous collection of free-living movement t ([Hernández-Hernández and Díaz-González, 2017](#)). However, an important limitation of device-based methods, is that they do not offer information on the context of PA or SB. As such, whilst device-based measures offer important insights into levels and patterns of PA and SB, self-report methods are able to capture more context and provide detail regarding personal experiences, perceptions, and contextual influences on behaviour.

## Measurement and prevalence of physical activity and sedentary behaviour in RA

In the past, self-report questionnaires have been the method most commonly used for studying PA and SB in RA, due to their cost effectiveness and ease of use. However, these retrospective self-report measures often suffer from poor validity and reliability ([Davergne et al., 2020](#); [Steultjens et al., 2023](#)). Still, most evidence on the relationship between SB and PA in RA is based on studies that rely on self-report methods to quantify engagement in these behaviours ([Fenton, Van Zanten, et al., 2018](#); [Verhoeven et al., 2016](#)). Devices such as accelerometers, offer a more valid and reliable measure of PA and SB compared to self-report tools ([Chastin et al., 2018](#)) Indeed, accurately measuring PA and SB is crucial for understanding the prevalence of physical inactivity and high SB, and the possible impact of these behaviours on RA outcomes. As such, device-based measure such as accelerometry, are preferred over self-reported questionnaires or diary-based approaches ([Steultjens et al., 2023](#)) for research in RA. Consequently, there is an increasing use of devices to measure PA and SB in RA research ([Fenton, Veldhuijzen van Zanten, et al., 2018](#)). To enable accurate measurement of these behaviours' researchers have sought to validate device-based methods for measurement of PA and SB in RA. For example, a previous study has affirmed activPAL as the gold standard for assessing living SB in individuals with RA ([O'Brien et al., 2020](#)), demonstrating classification accuracy for measuring sitting, standing and stepping >98%, when compared to direct observation. In addition, RA-specific accelerometer cut-points have been developed, to quantify time spent sedentary, and in light and moderate intensity PA ([O'Brien et al., 2020](#)).

Studies using device-based measures to examine levels of PA and SB and PA in individuals with RA have revealed that these patients tend to spend a significant portion of their day being sedentary (Paul et al., 2014; Prioreshi et al., 2013). Research has shown that patients with RA engage in prolonged periods of sitting with some spending over 18 hours a day in this position compared to individuals (Paul et al., 2014). In addition, study found that individuals with RA tend to be less physically active. Using a wrist worn accelerometer RA patients have been reported to have overall lower PA compared to the general population (Hashimoto et al., 2015). EULAR PA guidelines for people with inflammatory arthritis state that people with inflammatory arthritis, which includes RA, should adhere to the Public Health guidelines for PA, i.e., 150 minutes of moderate PA per week (Osthoﬀ et al., 2018). However, studies conducted in the UK reveal that a significant number of patients with RA fail to meet these PA recommendations (Schouller et al., 2019). This emphasises the need for interventions that focus on promoting PA and SB among this population.

### **The role of physical activity and sedentary behaviour in RA**

There is a wealth of research to date that demonstrates people living with RA greatly benefit from staying PA which helps reduce inflammation manage pain and maintain their mobility (Canning et al., 2022; Lee-Pii et al., 2020), which is also acknowledged in the EULAR for PA recommendations (Osthoﬀ et al., 2018). Engaging in PA not only enhances muscle strength and joint functionality but also boosts the overall quality of life for individuals with RA (Hernández-Hernández and Díaz-González, 2017; Ohenewa et al., 2021; Plasqui, 2008). In

addition, engaging in PA has shown to improve subclinical atherosclerosis, systemic inflammation and physical function among RA patients ([Hörnberg et al., 2019](#); [Kumalasari et al., 2023](#); [Metsios et al., 2009](#)). Additionally reduced PA has been associated with higher disease activity and limited functional capacity in RA patients ([El kabbaj et al., 2014](#)). Research suggests that regular exercise in particular, can play a role in managing RA by alleviating symptoms, reducing CVD risk, and improving overall wellbeing ([Canning et al., 2022](#)). These discoveries highlight the significance of PA in RA, including exercise, to improve RA symptoms and outcomes. Additionally participating in both resistance and aerobic exercise can positively impact cardiovascular disease risk factors and outcomes for those with RA ([Metsios et al., 2019](#)). However, despite these advantages many individuals with RA struggle to maintain their PA due to a lack of guidance and concerns about worsening their symptoms ([Canning et al., 2022](#)). SB poses a concern in RA due to its link with increased inflammation observed in the general population, which is already elevated among people living with RA ([Fenton, Zanten, et al., 2017](#)). Relatively less studies have explored the role of SB in RA, when compared to PA and exercise, but the available evidence suggests that higher levels of SB are related to higher levels of pain, inflammation, and lower physical function and overall quality of life among people living with RA ([O'Leary et al., 2020](#)). In addition, higher levels of SB are associated with increased risk of CVD in RA ([Fenton, Veldhuijzen van Zanten, et al., 2017](#); [Summers et al., 2019](#)). Nonetheless the lack of research in this area means that exact impact of SB on disease related outcomes in RA remains unclear ([Fenton, Zanten, et al., 2017](#)).

## **Physical activity, sedentary behaviour and fatigue in RA**

Despite the high prevalence of fatigue in RA, the role of PA and SB for fatigue management are largely unknown. Some cross-sectional and longitudinal studies have reported higher levels of PA and exercise are associated with lower levels of fatigue in RA (Cooney et al., 2019; Mancuso et al., 2006; Reinseth et al., 2011; Rongen-van Dartel et al., 2014). In addition, higher levels of SB are associated with higher levels of fatigue in RA (Brady et al., 2021; O'Brien et al., 2021). However, some studies report no associations between PA and SB with fatigue in RA (O'Leary et al., 2020; Pinto et al., 2023).

Considering interventions, existing research shows divergent approaches have been adopted to combat fatigue in RA and have reported inconsistent findings (Cramp, 2019). For example, (Salmon et al., 2017) and (Neill et al., 2006) reported that PA interventions, such as impact low aerobic exercise can effectively reduce fatigue. In addition, (Katz et al., 2018) and (Durcan et al., 2014) developed PA and exercise intervention that were effective at reducing fatigue in RA. However, others have not reported effects of PA or exercise interventions on fatigue in RA (Knittle et al., 2015; Nordgren et al., 2015; Van Zanten et al., 2021).

Therefore, the overall aim of the thesis is to explore the associations between different aspects of fatigue with PA and sedentary behaviour with a focus on people living with RA. These associations will be explored using different methodological approaches, including a scoping review in RA (chapter 2), cross-sectional data collected in people with RA (chapter 3), and cross-

sectional data collected over the course of one week in healthy participants (chapter 4). Below is a brief overview of these chapters.

There currently exist three key reviews of the role of PA and exercise for fatigue in RA (Rongen-van Dartel et al., 2015; Santos, Duarte, Marques, et al., 2019; Santos et al., 2023). Whilst these reviews provide initial evidence of the benefits of PA and exercise for fatigue in this patient group, each review had a narrow focus (i.e., only interventions targeting physical activity or moderate-intensity exercise), and none included studies on SB. As a result, these reviews included a relatively low number of studies, and do not give a comprehensive overview of the literature on the role of PA, exercise, and SB for fatigue in RA. In **Chapter 2** of this thesis, a scoping review of the literature on both PA, exercise, and SB in RA, which included cross-sectional, longitudinal and intervention studies was conducted. It was also explored whether there were common features of successful interventions, for example, supervision of PA or exercise, and support for behaviour change.

Where the research suggests that higher levels of PA and exercise, and lower SB may be associated with less fatigue in RA, interventions to support PA/exercise and SB behaviour change may be beneficial for this patient group. However, patterns of PA and SB are complex, and most of the available research (including that covered in **Chapter 2**), has relied on estimates of habitual (daily) PA and SB to explore these associations (e.g. minutes/day). Using only aggregate measures of PA and SB does not accurately reflect the dynamic nature of these behaviours, and the possible implications of how diurnal variations in PA and SB may associate with variability in fatigue. Insights into these associations is crucial to inform the development of interventions,

which may be effective at targeting fatigue in RA. This scoping review revealed interesting information about the associations between fatigue and movement behaviours. However, it was interesting to note that the majority of the studies used a one-off assessment of PA, SB and/or fatigue. This is surprising given that all these outcomes are known to fluctuate between and even within days. Therefore, the following chapters focussed on these aspects in more detail.

In **Chapter 3** of this thesis, the aim was to (1) examine the diurnal patterns of PA and SB in people living with RA and (2) examine whether these diurnal patterns were associated with different aspects of fatigue in these patients. In this study, the activPAL was used, which has been validated for measurement of SB, standing and stepping (as an indicator of PA) in RA (O'Brien et al., 2020). To measure the multidimensional nature of fatigue, the MFI-20 was used (Smets et al., 1995).

Whilst it is important to recognise the dynamic nature of PA and SB in RA, the same is true for experiences of fatigue. Currently, most studies investigating the role of PA and SB for fatigue – both in the general population, and in RA – have relied on recall of feelings of fatigue over a retrospective time-frame (e.g. weeks, months) (Hewlett, Ambler, et al., 2011). When considering the role of PA and SB for fatigue in RA, it is likely that variation in these behaviours will lead to fluctuations in levels of fatigue, which cannot be accurately captured by “static” measures of fatigue (i.e., asking about an individual’s experience of fatigue over aggregated time frames). The approach of Ecological Momentary Assessment (EMA) is a technique for gathering data on peoples behaviours, emotions and experiences in their surroundings (Hoppmann and Ho, 2015). This approach has been applied in domains such as health (Kampshoff et al.,

2019) education (Carson et al., 2010) and studies on depression, among older adults (Kim et al., 2020). EMA relies on asking participants to respond to questions (e.g., asking about their current level of fatigue) in real time, and offers a understanding of behaviour dynamics in real world settings (Shiffman et al., 2008). Its application to fatigue research, could therefore yield insights for understanding the role of PA and SB for fatigue, where coupled real-time movement data, collected from accelerometers.

To date, few studies have employed EMA in PA/SB and fatigue research. One study has compared how people felt on different days (feelings of happiness, stress, energy and fatigue) and examined this in regard to variability in self-reported and device-assessed movement (Liao et al., 2017a). Another study found that feelings like fatigue and energy were reported both before and after people engaged in light or intense physical activities (Liao et al., 2017b). EMA has also been used in studies of OA, in which low levels of habitual PA were associated with high levels of momentary fatigue (Murphy et al., 2008).

Additionally, EMA has also been successfully utilised for measuring PA and SB in older adults (Maher et al., 2018).

In Chapter 3, we explored a static measure of multidimensional aspects of fatigue, to explore associations between PA, SB and fatigue in RA. The next step, would be to pilot an EMA protocol in people living with RA. However, the COVID-19 pandemic meant this was not possible, so in this thesis, an EMA protocol was piloted in an accessible sample of undergraduate students, with the aim of exploring associations between daily PA and SB, with variability in self-reported fatigue across the day. This study also examined associations between daily PA and SB with an aggregate measure of fatigue, whereby

participants reported their feelings of fatigue over the previous month. This enabled; 1) testing of a simple EMA protocol, which could be easily adapted and implemented in people living with RA, and 2) exploration of the extent to which results may differ according to whether more static or dynamic measures of fatigue are employed in research. Whilst our original plans to collaborate directly with RA patients were affected by the impact of COVID 19, undergraduate students offers a relevant population to study in regards to fatigue. Indeed, several studies have shown a prevalence of fatigue among students with rates as high as 45.8% among graduate students ([Lee et al., 2007](#)) and 83.5% among undergraduate students ([Amaducci et al., 2010](#)). These studies underline the value of using approaches such as EMA to understand the role of PA and SB for fatigue in student populations.

**CHAPTER 2: EXERCISE, PHYSICAL ACTIVITY AND SEDENTARY  
BEHAVIOUR ON FATIGUE IN RHEUMATOID ARTHRITIS: A SCOPING  
REVIEW**

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune joint disease characterized by chronic high-grade systemic inflammation, joint pain, decreased muscle strength and physical disability (Cooney et al., 2011). With a global prevalence of 0.4 – 1.3% in adults, RA is a common disease worldwide (Espinoza et al., 2021). In addition to the effects of RA on joints and physical disability, there are other extra-articular manifestations that contribute to poor patient outcomes. Critically, research suggests living with RA can lead to significantly impaired quality of life, with fatigue being a large contributor (Rupp et al., 2004) .

Fatigue has been reported in more than 80% of RA patients (Pollard et al., 2006), with approximately 40% of people living with RA experiencing persistent fatigue lasting for  $\geq 1$  year and 57% of RA patients identifying fatigue as the most debilitating symptom of their condition (Repping-Wuts et al., 2007).

Fatigue is a multidimensional, persistent symptom of RA, and is associated with increased pain, depression, and psychological stress, as well as reduced functional status and quality of life in this patient group (Nikolaus et al., 2010).

Hewlett and colleagues (2005) reported that while fatigue is the most problematic symptom for most RA patients, the patient experience is that it is often overlooked by healthcare professionals (Hewlett et al., 2005). Currently, RA is treated with a variety of medications that aim to improve symptoms and stop or decelerate structural joint damage.

Physical activity and exercise are potential non-pharmacologic therapies for the management of fatigue in RA (Metsios and Kitas, 2018; Winzenberg et al.,

2007). Indeed, there is ample evidence that physical activity and exercise have numerous health benefits for people living with RA, such as improving joint health, physical function, mobility, and psychological wellbeing, as well as reducing fatigue (Cramp, 2019; Cramp et al., 2013; Katz et al., 2018; Neill et al., 2006). It is therefore not surprising that engagement in regular physical activity and exercise has been recommended as part of the overall multidisciplinary management of RA patients. For example, the European Alliance of Associations for Rheumatology (EULAR) recommends physical activity as part of the standard of care for patients with RA (Gwinnutt et al., 2022). In addition, EULAR recently recommended the creation of personalised PA programmes and psychoeducational support for people living with RA, to encourage them to engage in consistent physical activity for long term benefits (Dures et al., 2023; Santos et al., 2023). However, there is limited information on the extent to which these treatments are effective at improving fatigue.

A recent umbrella review of two systematic reviews examined the effects of different types of physical activity and exercise on fatigue and reported that both aerobic exercise and physical activity programs reduce fatigue among people living with RA (Santos, Duarte, Marques, et al., 2019). Specifically, one systematic review examined the effects of physical activity and psychosocial interventions on fatigue, and the meta-analysis revealed physical activity programs significantly improved fatigue for people living with RA (Cramp et al., 2013). The second systematic review focused specifically on examining the role of moderate-to-high intensity aerobic exercise programs (i.e., achieving between 50% and 90% of maximum heart rate) on fatigue in RA. Meta-analysis results demonstrated exercise significantly improved fatigue, and that the

benefits were more frequently observed in the short term (e.g., 12 weeks) ([Rongen-van Dartel et al., 2015](#)). However, whilst these reviews provide initial evidence of the benefits of physical activity and exercise for fatigue in this patient group, each review had a narrow focus (i.e., only interventions targeting physical activity or moderate-intensity exercise), and as a result included a relatively low number of studies.

Incorporating other study designs into a review of the literature on both physical activity and exercise (e.g., cross-sectional, and longitudinal studies), will provide a more comprehensive overview of the literature in this area. In addition, no reviews have considered the role of sedentary behaviour (waking behaviour requiring  $\leq 1.5$  metabolic equivalents, and a sitting or reclining posture) ([Bames et al., 2012](#)) on fatigue in RA, which research shows is increasingly important to consider for RA outcomes ([Fenton and Kitas, 2016](#)).

The primary aims of this scoping review were therefore to systematically search the available literature to; 1) evaluate cross-sectional and longitudinal studies examining the associations between exercise, physical activity, and sedentary behaviour with fatigue among people living with RA, and 2) to explore the effects of interventions targeting these behaviours on fatigue in RA.

## **Methods**

### ***Literature Search***

In line with the PRISMA guidelines ([Moher et al., 2015](#)) and referring to the JBI Manual for Evidence Synthesis on Scoping Reviews ([Peters et al., 2022](#)) we followed their recommendations for steps, like formulating the research question

and search strategy well as reporting our findings thoroughly to uphold high standards in conducting our scoping review of the existing research literature.

A search of the empirical literature was undertaken on the 10<sup>th</sup> of January 2024 using the following online from six databases: Cochrane Library and Physiotherapy Evidence Database (PEDro), Cumulative Index to Nursing & Allied Health Literature (CINHAL PULS), PsycINFO (OVID), Embase (OVID), and Medline (OVID). To assist with the development of a search strategy, the PICO method was applied with amendments being made for each of the databases. (**See Appendix 1**).

#### ***Example search strategy for PsycINFO (inc. Medline)***

exp Rheumatoid Arthritis OR (arthriti\* adj2 rheumat\*).mp. **AND** Exercise OR ((physical\* or aerobic or fitness or strength\* or muscle\* or cardiovascular or motor or stretch\*) adj3 (exercis\* or train\* or activ\* or program\* or function\*)).mp. OR ((resistance or endurance or walk\* or run or cycle\* or jog\* or swim\* or Pilate or yoga\* or tai Chi\* or rehabilitation\* or water therap\* or hydrotherap\* or pooltherapy\*) adj3 (exercis\* or train\* or activ\* or program\* or function\* or gym\* or therap\*)).mp. OR exp Sedentary Behavior or ((sedentary or Sit\* or screen\*) adj3 (behaviour\* or behavior\* or time\* or lifestyle\*)).mp. **AND** exp Fatigue or (vitality\* or tired\* or weary\* or weariness\* or exhaustion\* or exhausted\*).mp.

(\*) Retrieves all possible suffixes, (exp) Retrieves a term and all narrower terms (explode), (mp) Searches multiple fields (title, abstract, MeSH) and (adj3) Finds terms within three words of each other (adjacency operator).

To be considered for inclusion, a study had to: (1) be accredited as a cross-sectional, longitudinal or intervention study that assessed fatigue and one of;

physical activity and/or, exercise, and/or sedentary behaviour as either primary or secondary outcome measure. For intervention studies, RCTs, quasi-randomised and controlled trials were included. (2) include adults (aged  $\geq 18$  years), (3) include patients with a diagnosis of RA. Where studies included RA in combination with other populations, the study was included if analyses were reported separately for the RA sample, (4) have the full text published in English. Review articles, poster presentations, and conference papers were excluded.

### ***Data Collection***

First, duplicate studies retrieved in the searches were identified and deleted. The titles, abstracts, and full text of each of the research studies were then independently evaluated by two reviewers' (SE and SB). Finally, full-text articles of the studies that the independent reviewers believed to meet the inclusion criteria were obtained. The reference lists of full-text articles were then manually cross-referenced to find any additional papers, which were then screened using the process outlined above. If the two independent reviewers were unable to agree on whether an article should be included, another independent reviewer's opinion sought (JVvZ or SF). Data were extracted by the same two independent reviewers (SE and SB).

### **Results**

The results of the PRISMA flowchart search process are shown in **Figure 2.1**. After removing duplicates and screening articles by titles and abstracts, 104 titles were considered relevant for full-text reading. 41 studies were included in the review, comprising 20 cross-sectional studies, 3 longitudinal studies, and 18

interventions studies. Detailed information about the cross-sectional and longitudinal studies is reported in **Table 2.1**, and details of the intervention studies is displayed in **Table 2.2**.

### **Cross-sectional and longitudinal studies**

#### ***Study focus:***

Of the 20 cross-sectional studies, the majority examined the association between physical activity and fatigue (n = 17), with some of these studies also focussing on exercise and/or sedentary behaviour. The three longitudinal studies investigated the relationships between physical activity and/or sedentary behaviour with fatigue.

#### ***Study location, sample size and participant characteristics:***

Overall, studies were conducted in Westernised countries (e.g., UK, USA, EU, Canada), with the remaining studies conducted in South Korea (n = 2) ([Lee et al., 2006](#); [Suh et al., 2019](#)), Turkey (n = 1) ([Baloglu et al., 2015](#)), Egypt (n = 1) ([Elsawy et al., 2021](#)) and Brazil (n = 1) ([Pinto et al., 2023](#)). The sample size of studies ranged from n = 10 to n = 5235, with samples typically larger in studies focussed on physical activity, compared to exercise and sedentary behaviour. The majority of studies included both male and female participants, with an average age of  $\geq 38$  years, and established RA with an average disease duration ranging from 7 to 24 years. Only one study included people with early RA (average disease duration of 3 years ([Elsawy et al., 2021](#))). Only 3 studies included exclusively female participants ([Elsawy et al., 2021](#); [Pinto et al., 2023](#); [Reinseth et al., 2011](#)).

### ***Study measures:***

Device-based and self-report methods were employed to measure exercise, physical activity, and sedentary behaviour, with self-report being the most common method of assessment. For studies focussed on exercise, methods of assessment typically included self-report (n = 3) ([Brady et al., 2021](#); [Greysen et al., 2019](#); [Lee et al., 2006](#)), or indicators of cardiorespiratory fitness (e.g., VO2 max n = 4 ([Cooney et al., 2019](#); [Demmelmaier et al., 2018](#); [Munsterman et al., 2013](#)) and VO2 peak ([Weinstein et al., 2009](#))).

Studies concentrating on physical activity most frequently employed self-report (physical activity n = 15 ([Baloglu et al., 2015](#); [Belza et al., 1993](#); [Brady et al., 2021](#); [Demmelmaier et al., 2018](#); [Elsawy et al., 2021](#); [Henchoz et al., 2012](#); [Katz et al., 2016](#); [Løppenthin et al., 2015](#); [Mancuso et al., 2006](#); [Munsterman et al., 2013](#); [Reinseth et al., 2011](#); [Sokka et al., 2008](#); [Suh et al., 2019](#); [Tournadre et al., 2019](#); [Weinstein et al., 2009](#)) with more recent studies employing devices (n = 5) ([Hegarty et al., 2015](#); [O'Leary et al., 2020](#); [O'Brien et al., 2021](#); [Pinto et al., 2023](#); [Rongen-van Dartel et al., 2014](#)). For sedentary behaviour, a comparable number of studies used self-report measures (n = 2) ([Brady et al., 2021](#); [Løppenthin et al., 2015](#)) and device-based measures (n = 3) ([O'Leary et al., 2020](#); [O'Brien et al., 2021](#); [Pinto et al., 2023](#)).

Where self-report was used to assess exercise and/or physical activity, measures were varied, and often non-validated questionnaires or single item questions were used. The most common validated measures for physical activity were the International Physical Activity Questionnaire (IPAQ, n = 5) ([Baloglu et al., 2015](#); [Demmelmaier et al., 2018](#); [Elsawy et al., 2021](#); [Katz et al.,](#)

2016; Suh et al., 2019) and the Paffenbarger Physical Activity and Exercise Index (PAEI, n = 2) (Belza et al., 1993; Mancuso et al., 2006). The most common measures used to assess fatigue in cross-sectional studies were Visual Analogue Scales (VAS, n = 7) (Baloglu et al., 2015; Demmelmaier et al., 2018; Henchoz et al., 2012; O'Leary et al., 2020; Reinseth et al., 2011; Sokka et al., 2008; Suh et al., 2019) and the Multidimensional Assessment of Fatigue scale (MAF, n = 6) (Belza et al., 1993; Cooney et al., 2019; Lee et al., 2006; Munsterman et al., 2013; O'Brien et al., 2021; Weinstein et al., 2009) was frequently employed in both cross-sectional and longitudinal studies.

### **Key results**

**Exercise:** Seven studies explored the associations between exercise and fatigue. Four studies revealed no association between exercise and fatigue (Demmelmaier et al., 2018; Greysen et al., 2019; Munsterman et al., 2013; Weinstein et al., 2009). Three studies reported that exercise was associated with lower fatigue either by reporting less fatigue in people who exercised compared to those who did not (Cooney et al., 2019; Lee et al., 2006) or by reporting a significant negative association between exercise and fatigue (Brady et al., 2021).

**Physical activity:** Overall, more consistent associations were reported between physical activity and fatigue, compared to exercise. Of the Twenty studies measuring physical activity, n = 13 (n = 11 cross-sectional (Belza et al., 1993; Brady et al., 2021; Hegarty et al., 2015; Henchoz et al., 2012; Katz et al., 2016; Løppenthin et al., 2015; O'Leary et al., 2020; Reinseth et al., 2011; Rongen-van Dartel et al., 2014; Sokka et al., 2008; Tournadre et al., 2019) and n = 2

longitudinal (Mancuso et al., 2006; O'Brien et al., 2021), reported a negative association between physical activity and fatigue. However, three cross-sectional studies (Demmelmaier et al., 2018; Munsterman et al., 2013; Suh et al., 2019) and one longitudinal study (Pinto et al., 2023) reported no such association. Three of the studies which measured physical activity and fatigue did not analyse the relationships between these variables (Baloglu et al., 2015; Elsayy et al., 2021; Weinstein et al., 2009).

Sedentary behaviour: Overall, three cross-sectional (Brady et al., 2021; Løppenthin et al., 2015; O'Leary et al., 2020) and two longitudinal (O'Brien et al., 2021; Pinto et al., 2023) studies explored the association between sedentary behaviour and fatigue, with mixed findings. Positive associations between sedentary behaviour and fatigue were reported in two studies (n = 1 cross-sectional (Brady et al., 2021) and n = 1 longitudinal (O'Brien et al., 2021)), and n = 2 cross-sectional studies and n = 1 longitudinal reported no associations between sedentary behaviour and fatigue (Løppenthin et al., 2015; O'Leary et al., 2020; Pinto et al., 2023).

## **Intervention studies**

### ***Study focus:***

Of the eighteen intervention studies, the majority investigated the effects of exercise on fatigue (n = 11) (Ambrosino et al., 2020; Azeez et al., 2020; Cooney et al., 2019; Harkcom et al., 1985; Kucharski et al., 2019; Neuberger et al., 2007; Neuberger et al., 1997; Noreau et al., 1995; Pukšić et al., 2021; Rall et al., 1996; Van Zanten et al., 2021). Two studies included both exercise and physical activity in their intervention (Mayoux-Benhamou et al., 2008; Nordgren

et al., 2015), and four studies investigated the effects of physical activity on fatigue (Feldthusen et al., 2016; Katz et al., 2018; Knittle et al., 2015; Li et al., 2020). One study included a sedentary behaviour intervention (Thomsen et al., 2017).

***Study location, sample size and participant characteristics:***

All studies were conducted in Westernised countries (e.g., UK, USA, EU, Canada). In general, studies included more female than male participants, with two studies including exclusively female participants (Harkcom et al., 1985; Pukšić et al., 2021). The typical average age of the sample was  $\geq 40$  years, with the exception of one study which included participants with an average age of 28 years (Ambrosino et al., 2020). Participants had established RA with an average disease duration ranging from 5 to 21 years. Only one study included people with early RA (median disease duration of 2 years (Azeez et al., 2020).

***Study measures and assessment time points:***

Changes in exercise, physical activity, and sedentary behaviour: the most common measures employed to determine changes in exercise behaviour were VO2 max (n = 10) (Azeez et al., 2020; Cooney et al., 2019; Harkcom et al., 1985; Kucharski et al., 2019; Neuberger et al., 2007; Neuberger et al., 1997; Nordgren et al., 2015; Noreau et al., 1995; Rall et al., 1996; Van Zanten et al., 2021) and grip strength (n = 5) (Azeez et al., 2020; Harkcom et al., 1985; Neuberger et al., 2007; Neuberger et al., 1997; Nordgren et al., 2015). Most interventions assessed changes in physical activity using self-report (n = 4) (Feldthusen et al., 2016; Knittle et al., 2015; Mayoux-Benhamou et al., 2008; Nordgren et al., 2015). Only n = 3 interventions used devices to assess

changes in physical activity or sedentary behaviour (pedometer n = 1 ([Katz et al., 2018](#)); accelerometer n = 1 ([Li et al., 2020](#)), the activPAL n = 1 ([Thomsen et al., 2017](#)).

Changes in fatigue: the most common measures used to assess fatigue in intervention studies were the Multidimensional Assessment of Fatigue scale (MAF, n = 5) ([Azeez et al., 2020](#); [Cooney et al., 2019](#); [Neuberger et al., 2007](#); [Neuberger et al., 1997](#); [Van Zanten et al., 2021](#)), Visual Analogue Scales (n = 5) ([Feldthusen et al., 2016](#); [Kucharski et al., 2019](#); [Nordgren et al., 2015](#); [Rall et al., 1996](#); [Thomsen et al., 2017](#)), the Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT, n = 3) ([Ambrosino et al., 2020](#); [Mayoux-Benhamou et al., 2008](#); [Pukšić et al., 2021](#)) and the Profile of Moods Scale (POMS, n = 2) ([Neuberger et al., 1997](#); [Noreau et al., 1995](#)).

Assessment time points: Assessments of exercise, physical activity, sedentary behaviour, and fatigue were conducted at baseline, and immediately following the end of the intervention programme for all studies, except one study which only assessed fatigue after the intervention ([Harkcom et al., 1985](#)).

Nine exercise studies included at least one short-term follow-up assessment of exercise and fatigue ( $\leq 12$  weeks) ([Ambrosino et al., 2020](#); [Azeez et al., 2020](#); [Cooney et al., 2019](#); [Harkcom et al., 1985](#); [Neuberger et al., 2007](#); [Neuberger et al., 1997](#); [Noreau et al., 1995](#); [Pukšić et al., 2021](#); [Rall et al., 1996](#)), and four of these also included long-term follow-up of up to 52 weeks ([Neuberger et al., 1997](#); [Noreau et al., 1995](#); [Pukšić et al., 2021](#); [Van Zanten et al., 2021](#)). One exercise study only conducted longer-term follow-up assessments, at 20 and 52 weeks ([Kucharski et al., 2019](#)). The two studies that included both exercise and

physical activity included longer-term follow-ups of exercise, physical activity and fatigue: one at 48 weeks (Nordgren et al., 2015), and the other at 26 weeks (Mayoux-Benhamou et al., 2008). For physical activity interventions, three studies completed short-term follow-up assessments of physical activity and fatigue ( $\geq 12$  weeks) (Feldthusen et al., 2016; Knittle et al., 2015; Li et al., 2020), with one study conducting a short-term follow-up of fatigue, but not physical activity (Katz et al., 2018). Three of the physical activity interventions included a long-term follow-up of both physical activity and fatigue between 21 and 32 weeks (Feldthusen et al., 2016; Katz et al., 2018; Knittle et al., 2015). The only intervention targeting sedentary behaviour included a follow-up assessment of sedentary time and fatigue at 16 weeks (Thomsen et al., 2017).

#### **Intervention content:**

##### ***Exercise interventions:***

Aerobic training was prescribed in all eleven exercise interventions, but the content of the training in terms of the type of activity (e.g., swimming, cycling, walking, strengthening, /resistance exercise, yoga, wii-Fit), and the frequency, intensity and duration of the sessions varied substantially between studies (**see Table 2.2**). Programme session duration ranged from 15 to 90 minutes, target intensity from 50% to 89% of heart rate (or 1 rep) max, and frequency from 2-7 sessions/week. Most commonly, sessions lasted between 45 and 60 minutes (n = 6) (Ambrosino et al., 2020; Cooney et al., 2019; Neuberger et al., 2007; Neuberger et al., 1997; Rall et al., 1996; Van Zanten et al., 2021), with an intensity of  $\geq 55\%$  of heart rate max (n = 6) (Cooney et al., 2019; Harkcom et al., 1985; Kucharski et al., 2019; Neuberger et al., 2007; Neuberger et al., 1997;

Van Zanten et al., 2021), and a frequency of 2-3 times a week (n = 9)(Cooney et al., 2019; Harkcom et al., 1985; Kucharski et al., 2019; Neuberger et al., 2007; Neuberger et al., 1997; Noreau et al., 1995; Pukšić et al., 2021; Rall et al., 1996; Van Zanten et al., 2021). Programme duration ranged from 8 weeks to 20 weeks, with 12 weeks being the most common intervention length (n = 8) (Azeez et al., 2020; Harkcom et al., 1985; Neuberger et al., 2007; Neuberger et al., 1997; Noreau et al., 1995; Pukšić et al., 2021; Rall et al., 1996; Van Zanten et al., 2021).

Exercise supervision: In eight studies, each exercise session was supervised (Azeez et al., 2020; Cooney et al., 2019; Harkcom et al., 1985; Kucharski et al., 2019; Neuberger et al., 1997; Noreau et al., 1995; Pukšić et al., 2021; Rall et al., 1996) and two studies included non-supervised exercise (Ambrosino et al., 2020; Van Zanten et al., 2021). One study included one intervention group with supervised exercise and another intervention group with non-supervised exercise (Neuberger et al., 2007). There was variability in who supervised the exercise sessions, including physiotherapist (n = 2) (Azeez et al., 2020; Kucharski et al., 2019), research team (n = 2) (Harkcom et al., 1985; Rall et al., 1996), trained instructor (n = 1) (Pukšić et al., 2021), exercise physiologist (n = 1) (Cooney et al., 2019), multidisciplinary team (n = 1) (Noreau et al., 1995) and four studies did not specify who supervised the exercise sessions (Ambrosino et al., 2020; Neuberger et al., 2007; Neuberger et al., 1997; Van Zanten et al., 2021).

Behaviour change support: Only two of the intervention studies provided behavioural support to participants with RA (Noreau et al., 1995; Van Zanten et al., 2021). One study included weekly group counselling sessions which

included education related to RA, medication, pain, stress, fitness, and nutrition, followed by sharing experiences of the group members (Noreau et al., 1995).

The other involved a non-supervised exercise program with face-to-face and phone consultations conducted by a behaviour change counsellor at five time points during the intervention. The theory informed consultations (grounded in Self-Determination Theory) included aspects such as experience towards physical activity, education about physical activity for RA (including benefits, risks), patient-centred goal setting, problem solving to overcome barriers (Van Zanten et al., 2021).

### ***Exercise and physical activity interventions:***

Two interventions focussed on both increasing exercise and physical activity. In one intervention, the overall target was to promote Health-Enhancing Physical Activity (HEPA) and included a structured aerobic and resistance exercise programme similar to the programmes in the exercise only interventions (i.e., 45-minute sessions, targeting  $\geq 50\%$  heart rate max, 2 days a week). This intervention also encouraged participants to undertake >30 minutes of moderate intensity physical activity on most days (Nordgren et al., 2015). The other intervention involved home-based exercise, with a mix of range-of-motion exercises, strengthening exercises, and foot exercises (foot-roll and towel grabbing). Participants were asked to complete 3 out of the 10 available exercises each day. They were also asked to increase physical activity as part of daily living, with the target being a >20% increase relative to their baseline physical activity levels (Mayoux-Benhamou et al., 2008).

Exercise and physical activity supervision: in both of these interventions, the physical activity element was not formally supervised (Mayoux-Benhamou et al., 2008; Nordgren et al., 2015). In one study, exercise was not formally supervised, but an instructor was available at fixed times for advice on their programme (Nordgren et al., 2015). The other study included non-supervised home-based exercise (Mayoux-Benhamou et al., 2008).

Behaviour change support: both interventions included educational group sessions to support physical activity and exercise (Mayoux-Benhamou et al., 2008; Nordgren et al., 2015). More specifically, they both included information to develop behavioural skills to be more physically as well as the overall benefits of physical activity, and participants received booklets with this information. In addition, one of the studies also include information on RA and its management (Mayoux-Benhamou et al., 2008). The components of only one of the interventions was theory-informed (by Social Cognitive Theory) (Nordgren et al., 2015).

### ***Physical activity interventions:***

Of the four interventions focussed on physical activity, various physical activity targets were used. These included personalised targets referring to the physical activity public health guidelines (Feldthusen et al., 2016), encouraging general increases in the duration, frequency, and intensity of physical activity (Knittle et al., 2015), to increase daily step count by 10% every 2 weeks (Katz et al., 2018), and individualised targets without specification (Li et al., 2020).

Physical activity supervision: None of the interventions included supervision of physical activity.

Behaviour change support: Two physical activity interventions included provision of behavioural support for physical activity, comprising a group education session followed by individual sessions delivered either face-to-face or by phone. Individual sessions used a range of behaviour change techniques to support self-regulation skills, including action planning, goal setting, review of goals, barrier identification, monitoring of behaviour (Knittle et al., 2015; Li et al., 2020). One of these interventions was based on Self-Regulation Theory (Knittle et al., 2015). Another physical activity intervention included three different intervention groups, all with differing levels of support for physical activity in a step-wise manner. Specifically, all 3/3 groups were provided with an education booklet and guided discussion about physical activity, 2/3 groups also received a pedometer to monitor behaviour, and 1/3 groups also received an individualised review of goals by phone (Katz et al., 2018). The interventions were delivered by a physiotherapist (Li et al., 2020), different members of the multidisciplinary team including rheumatologist, nurse and psychologist (Knittle et al., 2015) and not known (Katz et al., 2018).

***Sedentary behaviour interventions:***

Only one intervention exclusively targeted sedentary behaviour. This intervention involved individual motivational counselling sessions to support people with RA to reduce daily TV viewing, and to substitute sitting (and break-up prolonged sitting) with standing (Thomsen et al., 2017).

Sedentary behaviour supervision: No element of behavioural supervision was delivered as part of the intervention.

Behaviour change support: The intervention included face-to-face support delivered via motivational counselling sessions and weekly text message reminders to reduce sitting time by a nurse or occupational therapist (Thomsen et al., 2017).

### **Key results:**

**Exercise:** Overall, of the eleven interventions targeting exercise, eight induced significant increases in their exercise-related outcome (e.g., n = 7 VO<sub>2</sub>max (Azeez et al., 2020; Cooney et al., 2019; Harkcom et al., 1985; Kucharski et al., 2019; Neuberger et al., 2007; Neuberger et al., 1997; Noreau et al., 1995), n= 3 muscle strength (Cooney et al., 2019; Noreau et al., 1995; Rall et al., 1996), and n = 4 grip strength (Azeez et al., 2020; Harkcom et al., 1985; Neuberger et al., 2007; Neuberger et al., 1997). For two interventions, the exercise was based on allocation (Ambrosino et al., 2020; Pukšić et al., 2021) and one reported no significant physiological effect of exercise (Van Zanten et al., 2021). Most of the interventions which successfully improved exercise included a supervised component (n = 6) (Azeez et al., 2020; Cooney et al., 2019; Kucharski et al., 2019; Neuberger et al., 1997; Noreau et al., 1995; Rall et al., 1996), except for one which did not include supervised exercise (Neuberger et al., 2007).

Of the eight (Azeez et al., 2020; Cooney et al., 2019; Harkcom et al., 1985; Kucharski et al., 2019; Neuberger et al., 2007; Neuberger et al., 1997; Noreau et al., 1995; Rall et al., 1996) interventions which demonstrated an increase in exercise, only n = 5 (Azeez et al., 2020; Cooney et al., 2019; Kucharski et al., 2019; Neuberger et al., 1997; Rall et al., 1996) also reported significant

changes in fatigue. For the interventions which provided behavioural support, only one increased exercise, and did not change fatigue (Noreau et al., 1995).

### ***Exercise and physical activity:***

Of the two interventions targeting exercise and physical activity, both studies successfully increased exercise (Mayoux-Benhamou et al., 2008; Nordgren et al., 2015), but only one study also increased physical activity (Mayoux-Benhamou et al., 2008). Both of these interventions included elements of behavioural support. The study which successfully increased physical activity and exercise, also improved fatigue (Mayoux-Benhamou et al., 2008).

**Physical activity:** All four of the physical activity interventions reported significant improvements in physical activity outcomes, two of which included behavioural support (Knittle et al., 2015; Li et al., 2020). However, only two of the successful physical activity interventions also reported significant improvements in fatigue (Feldthusen et al., 2016; Katz et al., 2018), and neither of these two interventions included supervision or behavioural support.

**Sedentary behaviour:** The one intervention targeting sedentary behaviour, reported a significant effect of the intervention on sedentary behaviour and fatigue (i.e. decreased sedentary behaviour and improved fatigue). As above, this intervention was not supervised, but did include support for behaviour change (Thomsen et al., 2017).

## **Discussion**

This review included 41 studies that examined the potential role of exercise, physical activity, and sedentary behaviour for improving fatigue among people

living with RA. To our knowledge, this is the first review to comprehensively examine different study designs (cross-sectional, longitudinal and intervention), to understand the role of these behaviours for fatigue in people living with RA.

Overall, observational studies included in this review do not provide a clear indication as to whether exercise is associated with fatigue in RA. However, these studies do indicate that higher physical activity was associated with lower levels of fatigue in this patient group. The differences observed between exercise vs. physical activity, may be due to the manner in which exercise vs. physical activity are typically assessed within these studies. For example, when measuring exercise, participants are frequently asked to indicate their levels of exercise engagement in reference to categories (e.g., yes/no to meeting physical activity guidelines, or engagement in <30 mins/day vs. 1 hour/day vs. >2 hours/day). In contrast, physical activity is often assessed using measures that enable physical activity levels to be quantified in a more linear and continuous fashion (e.g., total minutes/day). The approach used to measure physical activity, either device-based or subjectively, allows greater variability in physical activity levels to be captured, meaning associations with fatigue are more likely to be identified.

The majority of the observational studies included in this review were cross-sectional, with only three longitudinal studies exploring associations between physical activity and/or sedentary behaviour with fatigue ([Mancuso et al., 2006](#); [O'Brien et al., 2021](#); [Pinto et al., 2023](#)). More longitudinal studies, especially those devoted to exercise and sedentary behaviour, will provide more insight into whether variability in exercise, physical activity and sedentary behaviour relate to changes in fatigue in RA. In addition, studies which apply more novel

methodologies and statistical approaches – such as Ecological Momentary Assessment (EMA) and multi-level modelling - will represent an important advancement in this area (Fenton et al., 2020). These approaches will enable the dynamic between and within- person changes in movement behaviours and fatigue to be explored at a more granular level (e.g. day-to-day), and may offer important insights for the design of future interventions targeting fatigue in RA. However, observational research still does not allow us to establish cause and effect, thus, pointing to the importance of interventions to determine the role of exercise, physical activity, and sedentary behaviour for fatigue in RA.

Approximately half of the exercise interventions reported significant increases in exercise, and associated reductions in fatigue. However, interventions have varied widely in study design, program characteristics, support, duration, and exercise target groups, making overall interpretation of the results difficult. Still, this review has highlighted two major findings which are consistent across exercise interventions examined. First, a strength of this review is that we included exercise interventions targeting any type of exercise (e.g. aerobic, resistance, yoga). We found that the majority of the exercise interventions focussed on aerobic exercise training, with relatively fewer targeting resistance or other types of structured exercise. Given that exercise modality may influence the effectiveness of the intervention, and effectiveness may vary across RA outcomes (e.g. aerobic may improve CVD, and strength may improve function), exercise type should be considered in intervention design, and informed by the primary outcomes/goal of the intervention. Additionally, more research examining specific exercise types should be conducted to

elucidate the value of different exercises, which in turn could inform intervention design and recommendations.

Second, supervision of exercise appeared to result in more successful interventions when considering increasing levels of exercise and reducing fatigue ([Kelley et al., 2018](#); [Rongen-van Dartel et al., 2015](#)). Prior research exploring the question as to whether supervised exercise is superior to non-supervised exercise is scarce in patients with RA. However, our findings are in general agreement with a meta-analysis of RCTS, observed that supervised exercise programmes are more effective for improving aerobic capacity, when compared to unsupervised, home-based exercise in people living with RA ([Rongen-van Dartel et al., 2015](#)). In a sensitivity analysis, this study also found a somewhat larger reduction in fatigue (not significant) in a study with longer (24 weeks) vs. several studies with a shorter (< 12 weeks) period of supervision ([Rongen-van Dartel et al., 2015](#)). In addition, a previous RCT found that supervised, individualised aerobic and resistance training can lead to significant improvement in cardiorespiratory fitness (CRF) in RA patients ([Stavropoulos-Kalinoglou et al., 2013](#)). Interestingly, a subsequent RCT that used the same exercise component, but not under supervision, and did not improve CRF in RA patients ([Van Zanten et al., 2021](#)). As such, exercise supervision may be an important component to include in interventions aiming to improve any RA outcomes, through increasing levels of engagement in exercise.

Relative to exercise, fewer interventions focussed specifically on increasing physical activity. However, 3 out of 4 interventions (75%) targeting physical activity reported significant increases in physical activity and improvements in

fatigue post-intervention ([Feldthusen et al., 2016](#); [Katz et al., 2018](#); [Mayoux-Benhamou et al., 2008](#)). Considering that only (<50%) of exercise interventions included in this review were successful at increasing exercise and improving fatigue, it could be argued that physical activity interventions may be relatively more effective at improving fatigue in RA. However, the higher success of physical activity interventions is more likely to do with ability of interventions to successfully increase physical activity in RA, rather than the effectiveness of the exercise vs. physical activity for reducing fatigue, per se. Indeed, commonly reported barriers to exercise in RA include fatigue and pain, which may be less salient obstacles to increasing overall physical activity through activities such as walking, rather than structured exercise. Also interesting to note is that physical activity interventions were not supervised, suggesting that supervision may not be an important component for physical activity interventions. This may have implications when considering the design of interventions, making physical activity interventions more cost-effective than exercise interventions requiring supervision.

Our review also suggests that interventions which include behavioural support for exercise and/or physical activity engagement may be particularly effective. Our review identified only 6 interventions (two exercise ([Noreau et al., 1995](#); [Van Zanten et al., 2021](#)), two exercise and physical activity ([Mayoux-Benhamou et al., 2008](#); [Nordgren et al., 2015](#)), and 2 physical activity only ([Knittle et al., 2015](#); [Li et al., 2020](#))) which included elements of behavioural support, and the majority of these interventions (5/6, 83%) significantly increased levels of exercise and physical activity ([Knittle et al., 2015](#); [Li et al., 2020](#); [Mayoux-Benhamou et al., 2008](#); [Nordgren et al., 2015](#); [Noreau et al., 1995](#)). Research in

other patient groups consistently reports that interventions including support for behaviour change, can be effective at encouraging adoption of exercise and physical activity behaviour. For example, a systematic review of diet and physical activity interventions in Type 2 Diabetes, indicated that the use of specific behaviour change techniques (e.g. instruction on how to perform a behaviour and action planning), as well as intervention features such as supervised physical activity and group sessions, were associated with significant reductions in HBA<sub>1c</sub> (Cradock et al., 2017). In addition, a systematic review of physical activity interventions in hospitalised patients, reported that targeted behaviour change interventions were associated with increases in physical activity (Taylor et al., 2022). As such, including purposely designed support for behaviour change in exercise and physical activity interventions, may be instrumental to their success.

However, whilst the majority of the interventions including support for exercise/physical activity behaviour change in this review were largely effective, only one intervention reported parallel improvements in fatigue. It is therefore not clear if the changes in exercise and physical activity that were brought about through these interventions, were large enough (e.g. enough of a biological or psychological “signal”) to result in related improvements in fatigue. The quality of the study design in regard to the behavioural support offered may be critical to consider in this regard. For example, several reviews clearly outline that interventions which are grounded in psychological theory (i.e. theory-based), and utilise evidence-based behaviour change techniques linked to psychological determinants of behaviour, are likely to be more effective than those which do not take such an approach (Demmelmaier et al., 2018; Fenton

[et al., 2020](#); [Larkin et al., 2015](#)). Future interventions should therefore follow guidelines for proper integration of psychological theory into interventions design, delivery and evaluation, to optimise their potential efficacy.

Whilst the focus of this review was on the effects of exercise, physical activity, and sedentary behaviour on fatigue, only a few studies were directly concerned with sedentary behaviour. Additional research examining the role of sedentary behaviour for fatigue in RA is therefore warranted, particularly in the form of interventions. Indeed, only one intervention examined the effects of reducing sedentary behaviour on fatigue in RA, and results suggest that there may be value in interventions targeting sedentary time for improving fatigue in RA ([Thomsen et al., 2017](#)). It will be critical for future research to design studies and plan analysis to determine how sedentary time reductions may operate both independently, and interdependently with inter-related and parallel changes in physical activity frequency, intensity, and duration with behavioural support.

Our review also highlighted that the body of research examining the role of exercise, physical activity, and sedentary behaviour or fatigue in RA patients is characterised by methodological weaknesses in the measurement of these variables. Specifically, in our review, RA -related fatigue was measured using 16 different instruments in observational studies and 13 different instruments in intervention studies. Previous research has shown that fatigue associated with RA is a multidimensional symptom that includes physical, cognitive/emotional functioning and social aspects ([Nikolaus, 2012](#)). Theoretically, different domains of RA -related fatigue could be improved by modulating the effects of different interventions. For example, it is plausible that exercise may primarily improve

the physical dimension of RA -related fatigue, while other dimensions, such as mental fatigue, may be more responsive to behavioural interventions such as those targeting sedentary behaviour. Given the variety of instruments available, most meta-analyses available to date have combined the effects of physical activity and exercise on total RA-related fatigue. For this reason, future studies should clarify the quality of evidence on the validity and reliability of the different instruments measuring RA -related fatigue as SB post-intervention.

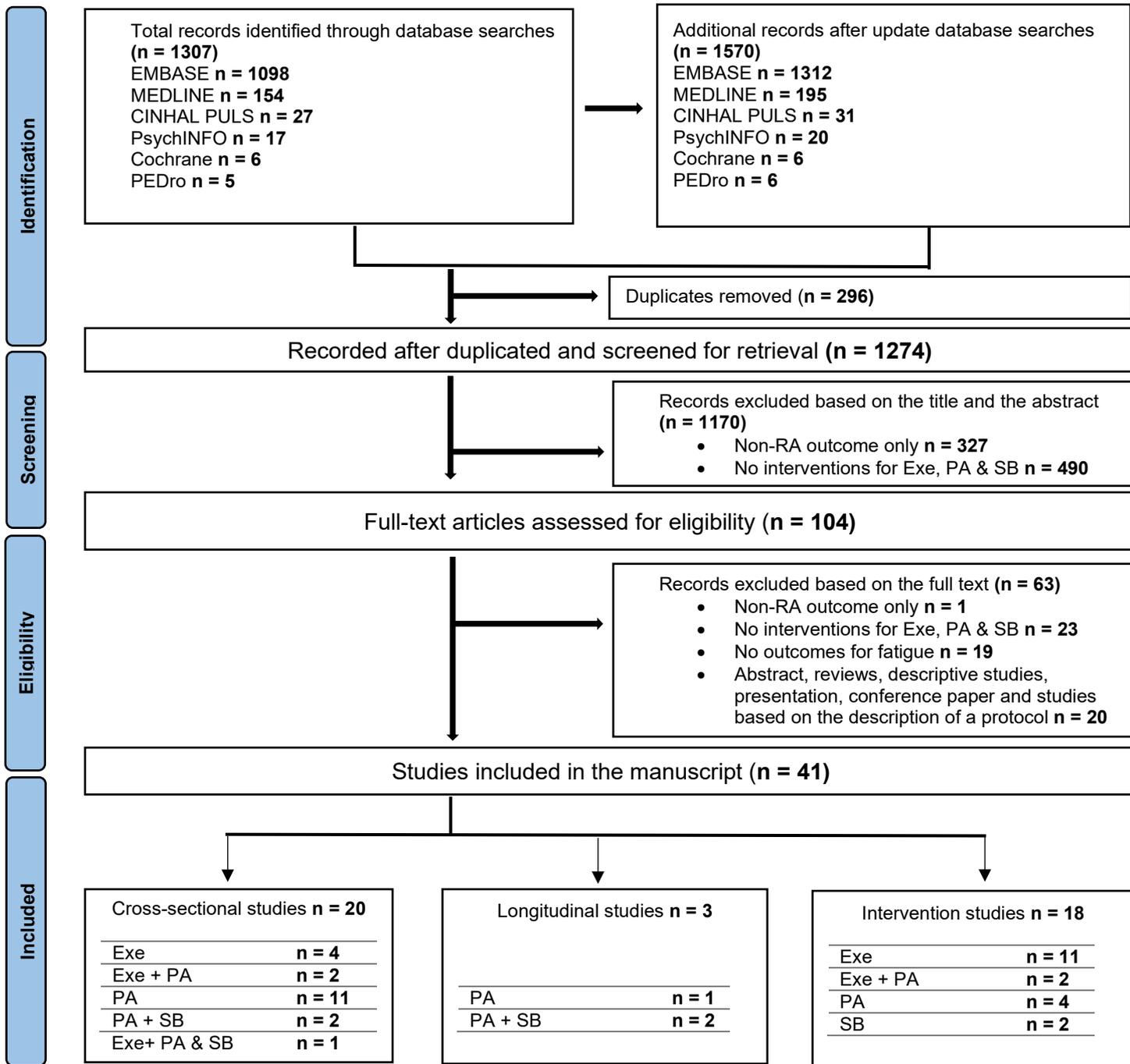
Whilst some interesting insights can be derived from the studies included in this review, some key limitations should be acknowledged. First, due to the relatively small sample sizes of included interventions studies, extrapolation of findings should be undertaken cautiously. Second, for interventions, comprehensive reporting of exercise protocols and participant adherence rates is essential to understanding the effectiveness exercise, and the required frequency, intensity, and duration to achieve improvements fatigue. Additionally, reporting of adherence data is essential to appraise the efficacy of exercise-based programmes. However, these data were not reported consistently in studies included, and future research should seek to address these methodological and reporting issues.

## **Conclusions**

To the best of our knowledge, this is the first review evaluating and examining exercise, physical activity, and sedentary behaviour with fatigue among people living with RA. Results from both observational and intervention studies suggest that there is likely a positive association and/or impact of exercise and physical activity on fatigue, but the relative efficacy of these behaviours needs to be

explored. The design of interventions is critical to consider in this regard, as supervision may be particularly important for exercise interventions, and behavioural support is likely to be a key component contributing to effectiveness across both intervention types. There is very limited evidence for the role of sedentary behaviour on fatigue in RA, but available results are promising. Further research using more harmonised methodologies is needed to gain a better understanding of the relationship between these behaviours and fatigue in individuals with RA, particularly from intervention studies.

**Fig.2.1:** PRISMA process of study selection



**Note:** RA = Rheumatoid Arthritis, Exe = Exercise, PA = Physical Activity, SB = Sedentary Behaviour.

Cochrane Library, (PEDro) = Physiotherapy Evidence Database, (CINHAL PULS) = Cumulative Index to Nursing & Allied Health Literature, (OVID) = PsycINFO, (OVID) = Embase, and (OVID) = Medline.

**Table 2.1:** Description of correlational and longitudinal studies

<i>Reference, location, and study design</i>	<i>Participant's characteristics</i>	<i>Study focus (Exe, PA, or SB) and aim</i>	<i>Measures</i>	<i>Key results</i>
(Lee et al., 2006) South Korea Cross-sectional	n = 435, 84% female, age 50 yr, disease duration 7 yr.	<b>Focus:</b> Exe <b>Aim:</b> Explored the associations between exercise with pain, fatigue, and disability.	<b>Behaviour:</b> Exe = participants defined based on level of exercise engagement: 1. "Exercisers" = self-reported exercise $\geq 3$ times/week for $\geq 20$ minutes, for $\geq 6$ months after diagnosis of RA. 2. "Non-exercisers" = did not meet "exercise" criteria.  <b>Fatigue:</b> Global Fatigue Index (Multidimensional Assessment of Fatigue (MAF) scale).	<b>T-tests</b> showed fatigue was <b>significantly</b> lower in participants classified as "Exercisers" compared to "non-exercisers".
(Cooney et al., 2019) United Kingdom Cross-sectional	n = 65, 71% female, age 58 yr, disease duration 10 yr.	<b>Focus:</b> Exe <b>Aim:</b> Examined associations between cardiorespiratory fitness and cardiovascular risk factors in RA.	<b>Behaviour:</b> Exe = cardiorespiratory fitness (Siconolfi step test).  <b>Fatigue:</b> Global Fatigue Index .	<b>N</b> = 10 participants completed 8 weeks of exercise (3 x week for 60 minutes at 55 - 85% HR max).  <b>T-tests revealed a significant</b> decrease in fatigue pre to post programme in these participants.
(Greysen et al., 2019) United States of America Cross-sectional	n = 269, 88% female, age 61 yr, disease duration 24 yr.	<b>Focus:</b> Exe <b>Aim:</b> Compared differences in RA outcomes (e.g., symptoms, function) according to yoga participation	<b>Behaviour:</b> Exe = reported participating in Yoga in the past year (yes, n = 42, vs. no n = 329).  <b>Fatigue:</b> Fatigue severity over the previous 2 weeks (single item rating of fatigue severity from 0 (no fatigue) to 5 (severe fatigue)	<b>T-tests</b> showed <b>no significant differences</b> between yoga and non-yoga participants.

(Weinstein et al., 2009)

United States of America

Cross-sectional

n = 10, 20% female, age 47yr, disease duration 8 yr.

**Focus:** Exe and PA  
**Aim:** Examined associations between PA, cardiorespiratory fitness, and fatigue in RA

**Behaviour(s):** Exe = **VO2 peak** (exercise tolerance test); PA = highest oxygen demanding self-reported activity the individual can perform (Maximum Activity Score from Human Activity Profile); self-reported usual daily activity (METS, Adjusted Activity Score from Human Activity Profile).

**Fatigue:** Global Fatigue Index (MAF scale) and fatigue severity (POMS-F).

**Correlational analyses** indicated **no significant association** between fatigue and Exe.

**No analysis** undertaken to examine associations between PA and fatigue.

(Demmelmaier et al., 2018)

Sweden

Cross-sectional

n = 269, 82% female, age 60 yr, disease duration 12 yr.

**Focus:** Exe and PA  
**Aim:** Explored the contribution of physical capacity (aerobic capacity, grip strength and timed standing) in explaining variations in fatigue among people with RA

**Behaviour:** Exe = VO2 max (submaximal Åstrand and Rhything bicycle ergometer test); PA = participants classified as meeting guidelines for Health Enhancing Physical Activity (Yes or No, International Physical Activity Questionnaire, IPAQ).  
\*\*Maintained HEPA (over the past 6 months) also assessed by the Exercise Stage Assessment Instrument.

**Fatigue:** Fatigue level (VAS-100). Fatigue was categorized as low/moderate (0–49 mm) or severe (50–100 mm).

**Logistic regressions** indicated **no significant relationships** between Exe and PA with fatigue.

**Adjusted logistic regressions** including variables, disease duration, biological. drugs, comorbidities, activity limitation, perceived health, pain, anxiety, depression, disease impact and physical capacity (grip strength, lower limb function, aerobic capacity) also indicated **no significant association** between Exe and PA with fatigue.

(Munsterman et al., 2013)	n = 60, 73% female, age 52 yr, disease duration 10 yr,	<b>Focus:</b> Exe and PA <b>Aim:</b> Explored whether low aerobic capacity and PA are associated with fatigue in RA.	<b>Behaviour(s):</b> Exe = VO2 max (submaximal walking test at self-selected walking speed between 3.2 and 7.2 km/hour); PA = MET hours/week (Short Questionnaire to Assess Health-enhancing physical activity, SQUASH).	<b>Bivariate correlations</b> showed Exe and PA <b>were not significantly related</b> to fatigue.  <b>Multiple regression analysis</b> indicated <b>no significant relationship</b> between Exe and PA with fatigue, when controlling for pain and depressive symptoms.
(Reinseth et al., 2011)	n = 238, 100% female, age 57 yr, disease duration 15 yr.	<b>Focus:</b> PA <b>Aim:</b> Examined the association between leisure-time PA and self-efficacy in females with RA.	<b>Behaviour:</b> PA = leisure time PA (The Interest Checklist). Participants were asked about leisure time PA performed, and activities divided into categories such as sports, conditioning exercises, household tasks and home repair. Participants who performed 0-4 activities defined as “less active,” vs. 5-9 activities defined as “active”.	<b>T-tests</b> showed fatigue was <b>significantly</b> lower in the “active” vs. “less active group”.  <b>Multiple logistic regression</b> reported a <b>significant</b> negative association between fatigue and leisure time PA (active vs. less active).
(Henchoz et al., 2012)	RA patients: n = 110, age ranged from 40-80 yrs. (mean not reported), 75% female, disease duration 9 yr. Controls: n = 440, ranged from 40-80 yrs., 75% female.	<b>Focus:</b> PA <b>Aim(s):</b> 1) compared daily energy expenditure between RA patients and controls, and 2) explored the relationship between daily energy expenditure or sedentariness with disease-related scores in RA.	<b>Behaviour:</b> PA = total energy expenditure over 7 days (Physical Activity Frequency Questionnaire). “Sedentary” individuals were defined as those expending <10% of total energy expenditure activities classed as having a Basal Metabolic Rate $\geq 4$ .  <b>Fatigue:</b> Fatigue level (VAS-10).	<b>T-tests</b> showed those classed as “sedentary” (based on total energy expenditure) reported significantly higher fatigue than those classed as “active”.  <b>Linear regression</b> revealed a significant negative association between total energy expenditure and fatigue. This association remained in multiple linear regression, which included age, RA duration, DAS-28, HAQ, and pain VAS.

(Hegarty et al., 2015)	n = 142, 67% female, age 62 yr, disease duration 17 yr.	<p><b>Focus:</b> PA</p> <p><b>Aim:</b> Examined whether daily PA moderated the within-person relationship between daily fatigue and positive or negative mood in RA.</p>	<p><b>Behaviour:</b> PA = steps/day (Braintek pedometer).</p> <p><b>Fatigue:</b> Fatigue level (self-reported in a diary daily, using a numerical rating scale ranging from 0 (“no fatigue”) to 10 (“totally exhausted”).</p>	<p><b>Multi-level modelling</b> indicated PA significantly moderated the relationship between daily fatigue and positive mood. Specifically, on low PA days, there was a significantly stronger relationship between fatigue and positive mood. This relationship was weaker but still significant on high PA days. (**the “low” and “high” activity days relate to each participant’s own average PA levels).</p>
(Sokka et al., 2008)	n = 5235, 79% female, age 57 yr, average disease duration not reported, but ranged from 9 to 15 yrs. depending on country.	<p><b>Focus:</b> PA</p> <p><b>Aim:</b> Examined the prevalence of PA, and associations with demographic and disease related variables in people with RA from 21 countries.</p>	<p><b>Behaviour:</b> PA = defined as &gt;30 min with at least some shortness of breath or sweating, with participants classed as either; &gt;3 times weekly, 1–2 times weekly, 1–2 times monthly (classed as no regular exercise) and no exercise (classed as physical inactivity, **question used in QUEST-RA study, not validated).</p> <p><b>Fatigue:</b> Fatigue score (VAS-10).</p>	<p><b>Generalized linear models</b> revealed physical inactivity was significantly more prevalent in patients with higher fatigue levels (adjusted for age and sex).</p>
(Katz et al., 2016)	n = 158, 85% female, age 59 yr, disease duration 21 yr.	<p><b>Focus:</b> PA</p> <p><b>Aim:</b> Explored potential risk factors for fatigue in RA.</p>	<p><b>Behaviour:</b> PA = total minutes of moderate-to-vigorous PA per week. Participants classified as either inactive (&lt;150 minutes/week) or active (≥150 minutes/week) (IPAQ).</p> <p><b>Fatigue:</b> Fatigue severity over the past week (Fatigue Severity Inventory).</p>	<p><b>Bivariate analysis</b> - physical inactivity was <b>significantly</b> positively associated with fatigue.</p> <p><b>Multivariate analysis</b> - physical inactivity was <b>not a significant</b> independent predictor of fatigue.</p> <p><b>Mediation analysis</b> - sleep quality, obesity, and depressive symptoms significantly mediated the effects of physical inactivity on fatigue.</p>

(Suh et al., 2019) South Korea Cross-sectional	n = 345, 88% female, age 52 yr, disease duration 7 yr.	<b>Focus:</b> PA <b>Aim:</b> Evaluated levels of PA and identified factors affecting a physically active lifestyle in RA.	<b>Behaviour:</b> PA = participants classed as “physically active” if they achieved > 600 MET-minutes/week (approximately = (150 minutes moderate-to-vigorous PA per week) and moderate activity or walking at least three times per week (IPAQ).  <b>Fatigue:</b> Fatigue level (Multidimensional Health Assessment Questionnaire, using a VAS-10).	<b>T-tests</b> indicated levels of fatigue were higher in those participants not classed as “physically active”, but <b>differences were not statistically significant.</b>
(Baloglu et al., 2015) Turkey Cross-sectional	n = 60,84% female, age 53 yr, disease duration 8 yr.	<b>Focus:</b> PA <b>Aim:</b> explored associations between several clinical RA symptoms and features (e.g., disease activities, laboratory values, radiographical damages), levels of PA, psychological functions, and perceived social support on health-related quality of life.	<b>Behaviour:</b> PA = participants classed as; physically inactive <600 MET-minutes/week), low PA (600-3000 MET-minutes/week), or sufficient levels of PA (> 3000 MET-minutes/week) (IPAQ).  <b>Fatigue:</b> Fatigue level (VAS-10).	<b>No analysis</b> undertaken to examine associations between PA and fatigue.
(Elsawy et al., 2021) Egypt Cross-sectional	n = 48 women with RA, 100% female, age 38 yr, disease duration 3 yr. Also included control group of n = 48 women without RA.	<b>Focus:</b> PA <b>Aim:</b> Determined the relation between the serum level of anti-carbamylated protein antibodies in premenopausal RA women and disease activity and bone loss.	<b>Behaviour:</b> PA = measured by the IPAQ, but outcome variable computed from this measure not reported. Participants only described as being classed as low, moderate, or high activity.  <b>Fatigue:</b> Fatigue level (Modified Fatigue Impact Scale).	<b>No analysis</b> undertaken to examine associations between PA and fatigue.

(Belza et al., 1993)	n = 133, 75% female, age 67 yr, disease duration 18 yr.	<b>Focus:</b> PA <b>Aim:</b> To examine the relationship between fatigue and use of healthcare services, and to identify the demographic, disease-related and psychosocial correlates of fatigue in RA.	<b>Behaviour(s):</b> PA = Energy expenditure as kcal/week (Paffenbarger Physical Activity and Exercise Index). <b>Fatigue:</b> Global Fatigue Index (MAF scale).	<b>Hierarchical multiple regressions indicated</b> PA (energy expenditure) was significantly negatively associated with fatigue and contributed 6% of the variance in fatigue (adjusted for age, sex, education, disease duration, pain, sleep quality, co-morbid conditions, and functional status).
United States of America				
Cross-sectional				
(Mancuso et al., 2006)	n = 122 people living with RA, 84% female, age 49 yr (at baseline) Also included control group of additional n = 122 people without RA, of similar age, sex, education, employment, and marital status.	<b>Focus:</b> PA <b>Aim:</b> Evaluated relationships between diverse psychosocial characteristics and fatigue among people living with RA.	<b>Behaviour:</b> PA = Energy expenditure as kcal/week (Paffenbarger Physical Activity and Exercise Index). <b>Fatigue:</b> Fatigue severity (Fatigue Severity Scale). <b>Assessments:</b> Baseline and 12-month follow-up	<b>Cross-sectional and longitudinal bivariate correlations</b> indicated lower PA was significantly positively associated with fatigue. <b>Cross-sectional and longitudinal multivariate regressions</b> indicated lower PA <b>was not significantly associated</b> with fatigue when adjusting for other measured variables (in multivariate models, follow-up fatigue score as the dependent variable and baseline PA as the independent variable).
United States of America				
Longitudinal				
(Tournadre et al., 2019)	n = 970, 79% female, age 57 yr, disease duration 11 yr.	<b>Focus:</b> PA <b>Aim:</b> Analysed the factors associated with fatigue in RA, focusing on comorbidities.	<b>Behaviour:</b> PA = participants were asked to self-report if they engaged in PA ≥30 minutes day (yes/no response, **question used in COMEDRA study, not validated) <b>Fatigue:</b> Fatigue level (question 3 of the Rheumatoid Arthritis Impact of Disease (RAID) score on a 0–10 numerical rating scale)	<b>Bivariate and multivariate regression analyses</b> demonstrated moderate and severe fatigue was <b>significantly</b> more frequent in those who answered “no” to engaging in ≥30 minutes of PA each day. (**results for severe fatigue reported in multivariate analysis only).
France				
Cross-sectional				

(Rongen-van Dartel et al., 2014)	<p>n = 167 with valid PA data. Participant characteristics reported according to activity level.</p> <p><b>Low activity:</b> n = 42, 79% female, age 57 yr, disease duration 10 yr.</p> <p><b>High activity:</b> n = 125, 54% female, age 55 yr, disease duration 10 yr.</p>	<p><b>Focus:</b> PA</p> <p><b>Aim:</b> Investigated whether daily PA is associated with fatigue in RA, and whether other RA factors are associated with daily PA.</p>	<p><b>Behaviour:</b> PA = accelerometer activity counts that was the weighted sum of the number of accelerations measured every 5-minutes (Actometer accelerometer). Low activity level participants were defined as those whose activity level was lower than the group average for at least 90% of the total observation period.</p> <p><b>Fatigue:</b> Fatigue severity (Checklist Individual Strength 20 questionnaire).</p>	<p><b>T-tests revealed</b> high PA patients had <b>significantly</b> lower fatigue scores than the low activity patients.</p> <p><b>Linear regressions</b> revealed a <b>significant</b> negative association between higher daily PA and reduced fatigue adjusted for age, sex, pain, body-mass-index, and physical function.</p>
(O'Brien et al., 2021)	<p>n = 102, with valid PA and SB data, 71% female, age 58 yr, disease duration 10 yr (at baseline).</p>	<p><b>Focus:</b> PA and SB</p> <p><b>Aim:</b> Examined the longitudinal and bi-directional associations between sedentary, standing and stepping time with pain and fatigue in RA.</p>	<p><b>Behaviour:</b> PA = stepping and standing time (minutes/day); SB = sitting time (minutes/day) – all ActivPAL4.</p> <p><b>Fatigue:</b> Global Fatigue Index (MAF Scale).</p>	<p><b>Cross-sectional bivariate correlations</b> indicated fatigue was <b>significantly</b> negatively related to standing and stepping time, but <b>was not significantly related to SB</b>.</p> <p><b>Longitudinal linear regressions</b> indicated change in fatigue was <b>significantly</b> negatively associated with change in standing time but <b>was not significantly associated</b> with change in stepping or sedentary time.</p> <p><b>Bi-directional path analysis</b> indicated fatigue showed a <b>significant</b> positive bidirectional association with sedentary time, and significant negative bi-directional relationships with standing time.</p>

(O'Leary et al., 2020)	n = 72 with valid PA and SB data, 65% female, age 62 yr, disease duration 18 yr.	<p><b>Focus:</b> PA and SB</p> <p><b>Aim:</b> Examined associations between PA and SB with a range of pain characteristics and RA-related symptoms</p>	<p><b>Behaviour:</b> <b>PA</b> = stepping and standing time (minutes/day), sedentary interruptions (number/day), <b>SB</b> = sitting time (minutes/day) and Sedentary bouts &gt;30 minutes (number/day) – all ActivPAL4).</p>	<p><b>Correlation analysis indicated</b> standing time (as an indicator of PA) was <b>significantly</b> negatively related to fatigue.</p>
Ireland			<p><b>Fatigue:</b> Fatigue severity over the past week (VAS-10).</p>	<p>Other PA or SB variables <b>were not significantly associated</b> with fatigue.</p>
Cross-sectional				
(Løppenthin et al., 2015)	n = 443, 80% female, age 60 yr, disease duration (median) 11 yr.	<p><b>Focus:</b> PA and SB</p> <p><b>Aim:</b> Examined PA behaviour and identified potential correlates of regular PA including fatigue, sleep, pain, physical function, and disease activity in RA.</p>	<p><b>Behaviour:</b> <b>PA</b> = Participants classed as low PA (suboptimal) PA, or regular (recommended) PA (Leisure Time Physical Activity Level questionnaire) and hours/day in light, moderate and vigorous PA (Physical Activity Scale); <b>SB</b> = hours/day sitting (Physical Activity Scale).</p>	<p><b>Mann-Whitney tests</b> indicated median scores for all fatigue dimensions were significantly lower among “regular” vs. “low” PA groups.</p>
Denmark			<p><b>Fatigue:</b> Fatigue severity in 5 domains; mental, motivation, activity, physical, general (Multidimensional Fatigue Inventory, MFI).</p>	<p><b>Logistic regression</b> - participants with a higher score on mental, reduced activity, physical and general fatigue, had significantly lower odds for being classed as “regular” PA than “low” PA.</p>
Cross-sectional				<p><b>Multivariate prediction model</b> indicated physical and reduced activity fatigue significantly predicted regular PA.</p>
(Brady et al., 2021)	n = 345, 93% female, age 51 yr, disease duration 11 yr.	<p><b>Focus:</b> Exe, PA, and SB</p> <p><b>Aim:</b> Investigated associations between PA and SB with indicators of mental health and wellbeing among people with RA, during the COVID-19 lockdown.</p>	<p><b>Behaviour:</b> <b>Exercise</b> (e.g., tennis, cycling) (National Institutes of Health-American Association of Retired Persons); <b>PA</b> = minutes/week spent in: 1) light-intensity PA (e.g., cooking, laundry) and (2) walking; <b>SB</b> = sedentary time (minutes/week, IPAQ)</p>	<p><b>Linear regressions</b> showed <b>significant</b> negative associations between:</p> <ul style="list-style-type: none"> <li>• Light-intensity PA and mental fatigue.</li> <li>• Walking and physical fatigue.</li> <li>• Exercise with physical and general fatigue.</li> </ul>
United Kingdom			<p><b>Fatigue:</b> Fatigue severity in 5 domains; mental, motivation, activity, physical, general (MFI)</p>	<p>Positive <b>significant</b> associations were found between SB with physical fatigue.</p>
Cross-sectional				

<p>(Pinto et al., 2023)</p> <p>Brazil</p> <p>Longitudinal (within-subjects repeated measures design, pre and post COVID social distancing).</p>	<p>n = 35, 100% female, age 60 yr, disease duration (median) 18 yr.</p>	<p><b>Focus:</b> Exe, PA, and SB <b>Aim:</b> Investigated associations between PA and SB with indicators of mental health and wellbeing among people with RA, during the COVID-19 lockdown</p>	<p><b>Behaviour:</b> <b>PA</b> = stepping and standing time (hour/day, ActivPALmicro™); <b>SB</b> = sitting time (hour/day, ActivPALmicro™).</p> <p><b>Fatigue:</b> Fatigue severity (Fatigue Severity Scale).</p> <p><b>Assessments:</b> Baseline (pre COVID social distancing) and 12-month follow-up (post-COVID social distancing).</p>	<p><b>Pearson correlation showed</b> PA and SB were not significant associated with fatigue.</p> <p>Changes in PA and SB (before vs. during social distancing) <b>were not associated with changes</b> in fatigue”.</p>
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- Note: **RA** = Rheumatoid Arthritis, **Exe** = Exercise, **PA** = Physical Activity, **SB** = Sedentary Behaviour.
  - For measures, methods or questionnaires used to assess behaviours (Exe, PA, and SB) and fatigue, are indicated in parenthesis. For results, significant associations are highlighted with bold text. Results that are not significant are highlighted with bold and underlined text.
  - Values for age and disease duration are mean values, unless otherwise stated (e.g., median).

**Table 2.2:** Description of intervention studies

<i>Reference, location, and intervention focus (IG vs. CG)</i>	<i>Participant characteristics</i>	<i>Intervention session details</i>	<i>Measures and assessment time points</i>	<i>Key results</i> 1. <i>Change in Exe, PA, and SB.</i> 2. <i>Change in fatigue.</i>
<p>(Azeez et al., 2020) Ireland RCT</p> <p><b>Focus:</b> Exe</p> <p><b>IG:</b> Personalised Exe programme (walking, cycling, or swimming, and strengthening).</p> <p><b>CG:</b> Usual care.</p>	<p><b>IG:</b> n = 28, 86% female, age 59 yr. disease duration (median) 2 yr.</p> <p><b>CG:</b> n = 24, 83% female, age 63 yr, disease duration (median) 9 yr.</p>	<p><b>SD</b> = Not stated. <b>Int</b> = Not stated. <b>Freq</b> = Not stated. <b>PD</b> = 12 weeks.</p> <p><b>Supervision:</b> Yes. <b>Support for behaviour:</b> No. <b>Specialist:</b> Physiotherapist.</p>	<p><b>Behaviour:</b> Exe =</p> <ul style="list-style-type: none"> <li>• VO<sub>2</sub> max (submaximal exercise test).</li> <li>• Grip strength.</li> </ul> <p><b>Fatigue:</b> Global Fatigue Index (MAF scale).</p> <p><b>Assessments:</b> Baseline and 12 weeks.</p>	<p>1. <b>Exe.</b></p> <ul style="list-style-type: none"> <li>• <b>Significant</b> improvements in VO<sub>2</sub>max in IG but not in CG.</li> <li>• <b>Significant</b> improvements in Right- and left-hand grip strength in IG but not in CG.</li> </ul> <p>2. <b>Significant</b> improvement in fatigue in IG, no change in CG.</p>
<p>(Harkcom et al., 1985) United States of America RCT</p> <p><b>Focus:</b> Exe</p> <p><b>IG:</b> Group aerobic Exe (cycling) – training schedule for groups based on baseline fitness.</p> <p><b>CG:</b> Continue routine daily activities.</p>	<p><b>IG:</b> n = 11, 100% female.</p> <p><b>Group A:</b> n = 4, age 51 yr, disease duration 12 yr.</p> <p><b>Group B:</b> n = 3, age 47 yr, disease duration 11yr.</p> <p><b>Group C:</b> n = 4, age 44 yr, disease duration 6 yr.</p> <p><b>CG:</b> n = 6, age 45 yr., disease duration 9 yr.</p>	<p><b>SD</b> = Gradual increase from 15 to 35 minutes. <b>Int</b> = 70% of HR max. <b>Freq</b> = 3 days/week. <b>PD</b> = 12 weeks.</p> <p><b>Supervision:</b> Yes. <b>Support for behaviour:</b> No. <b>Specialist:</b> Physical education graduate student.</p>	<p><b>Behaviour:</b> Exe =</p> <ul style="list-style-type: none"> <li>• VO<sub>2</sub> max (graded Exe tolerance test).</li> <li>• Grip strength.</li> </ul> <p><b>Fatigue:</b> Change in fatigue (“much better, better, same, worse”).</p> <p><b>Assessments:</b> Baseline (VO<sub>2</sub>max) and 12 weeks (VO<sub>2</sub>max, fatigue).</p>	<p>1. <b>Exe.</b></p> <ul style="list-style-type: none"> <li>• <b>Significant</b> improvement in VO<sub>2</sub>max in IG, no change in CG.</li> <li>• <b>Significant</b> improvements in grip strength improvement in IG, no change in CG.</li> </ul> <p><b>No statistical</b> analyses conducted on fatigue.</p>

(Neuberger et al., 1997)  
United States of America  
Quasi-experimental time  
series study

**Focus:** Exe

**IG:** Low-impact aerobic and  
resistance Exe class.

**IG:** n = 25, 24%  
female, age 55 yr.  
disease duration  
10 yr.

**SD** = 60 min.  
**Int** = 60 - 80% of HR max.  
**Freq** = 3 days/week.  
**PD** = 12 weeks.

**Supervision:** Yes.  
**Support for behaviour:** No.  
**Specialist:** Aerobic instructor.

**Behaviour:** Exe =

- VO<sub>2</sub> max (submaximal  
exercise test).
- Grip strength.

**Fatigue:** Fatigue distress,  
severity, timing, global fatigue  
scale (MAF scale, Profile of  
Mood States (POMS) fatigue  
scale)

**Assessments:** Baseline, 6  
weeks, 12 weeks, and 27  
weeks

**1 Exe.**

- **Significant** increase in VO<sub>2</sub> post  
intervention. But no difference in  
VO<sub>2</sub>max immediately post intervention  
and 15 weeks post intervention.
- **Significant** increase in Right- and left-  
hand grip strength post intervention and  
after 15 weeks post intervention.

**2 Significant** decrease in fatigue distress  
and severity subscales, but not timing,  
global fatigue, or POMS fatigue. No  
difference in fatigue immediately posts  
intervention and 15 weeks post  
intervention.

(Rall et al., 1996)  
United States of America  
RCT

**Focus:** Exe

**IG:** Progressive resistance  
strength Exe.

**CG:** (non-RA control groups  
with no fatigue assessment).

**IG:** n = 8 RA, 63%  
female, age 42 yr,  
disease duration  
14 yr.

**SD** = 45 minutes.  
**Int** = 80% of 1 rep max.  
**Freq** = 2 days/week.  
**PD** = 12 weeks.

**Supervision:** Yes.  
**Support for behaviour:** No.  
**Specialist:** Research team.

**Behaviour:** Exe =

- VO<sub>2</sub> max (exercise  
tolerance test),
- Strength (1-rep max of  
major muscle groups).

**Fatigue:** Fatigue level (VAS-  
15).

**Assessments:** Baseline and  
12 weeks.

**1 Exe.**

- **No significant** in VO<sub>2</sub>max IG.
- **Significant** increase in muscle strength  
in IG.

**2 Significant** decrease in fatigue in IG.

(Neuberger et al., 2007)  
United States of America  
RCT

**Focus:** Exe

**IG1:** Low-impact aerobic Exe class.

**IG2:** Home-based low-impact aerobic Exe.

**CG:** Continue routine exercise levels.

**Overall sample:** n = 220, 82% female, age 55 yr, disease duration (median) 8 yr.

**IG1:** n = 68.

**ICG2:** n = 79.

**CG:** n = 73.

**IG1: SD** = 60 minutes.  
**Int** = 60 - 80% of HR max.  
**Freq** = 3 days/week  
**PD** = 12 weeks.

**Supervision:** Yes.  
**Support for behaviour:** No  
**Specialist:** Instructor (specialty not stated).

**IG2: SD** = 60 minutes.  
**Int** = 60 - 80% of HR max.  
**Freq** = 3 days/week.  
**PD** = 12 weeks.  
**Supervision:** NO  
**Support for behaviour:** No.  
**Specialist:** Instructor (specialty not stated).

(Cooney et al., 2019)  
United Kingdom  
Longitudinal intervention  
(pre-post measures in one group).

**Focus:** Exe

**IG:** Aerobic Exe (treadmill, bike, rower, stepper, cross-trainer) and resistance Exe.

**IG:** n = 10, 80% female, age 64 yr, disease duration 11 yr.

**SD** = 60 minutes.  
**Int** = 55% - 85% HR max.  
**Freq** = 3 days/week.  
**PD** = 8 weeks.

**Supervision:** Yes.  
**Support for behaviour:** No.  
**Specialist:** Exercise physiologist.

**Behaviour:** Exe =  
• VO2 max (submaximal exercise test).  
• Grip strength.

**Fatigue:** Global Fatigue Index (MAF scale).

**Assessments:** Baseline, 6 weeks, 12 weeks.

**Behaviour:** Exe = VO2 max, (estimated from Siconolfi step test), leg strength (30-sec sit to stand test).

**Fatigue:** Global Fatigue Index (MAF scale).

**Assessments:** Baseline and 8 weeks.

**1 Exe.**

- **Significant** increase in VO2max (overall time effect), but no difference between groups.
- **Significant** increase in grip strength, but only group by time interaction effect for left grip strength.

Comparison of group effects on changes in fatigue not reported.

**1. Exe.**

- **Significant** increase in VO2max.
  - **Significant** increase in lower body strength.
- 2. Significant** improvement in fatigue.

(Noreau et al., 1995)  
Canada  
RCT

**Focus:** Exe

**IG:** Aerobic Exe (modified dance).

**CG:** Not stated.

**IG:** n = 19, 63% female, age 49 yr, disease duration 8 yr.

**CG:** n = 10, 80% female, age 49 yr, disease duration 11 yr.

**SD** = 25 - 55 minutes.  
**Int** = 50 increasing to 70% of HR max.  
**Freq** = 2 days/week Exe + 1 counselling session/week.  
**PD** = 12 weeks.

**Supervision:** Yes.  
**Support for behaviour:** Faces to face counselling and discussion session.  
**Specialist:** Physical therapist and Occupational therapist (Exe), Psychologist.

**Behaviour(s):** Exe = VO<sub>2</sub> max (exercise tolerance test), leg muscle strength (cybex II isokinetic dynamometer).

**Fatigue:** Fatigue severity (POMS).

**Assessments:** Baseline, 12 weeks, 26 weeks.

1. **Exe.**

- **Significant** increase in VO<sub>2</sub>max in IG, but not CG. Some improvements in muscle strength in IG and CG.

2. **No Significant** decrease in fatigue IG or CG.

(Kucharski et al., 2019)  
Sweden  
RCT

**Focus:** Exe

**IG:** Gym-based high-intensity aerobic and resistance Exe with light home-based Exe.

**CG:** Light home-based Exe for mobility, lower body strength and balance.

**IG:** n = 36, 75% female, age 69 yr, disease duration 15 yr.

**CG:** n=38,76% female, age 70 yr, disease duration 17 yr.

**IG:**  
**SD** = 27 minutes  
**Int** = 70% - 89% of HR max.  
**Resistance** = 70% – 80% of 1 rep max.  
**Freq** = 3 days/week.  
**PD** = 20 weeks.

**Supervision:** Yes.  
**Support for behaviour:** NO.  
**Specialist:** Physiotherapist.

**CG:**  
**SD** = not stated.  
**Int** = not stated.  
**Freq** = 2 days/week home exercises, 5 days/week low-intensity physical activities.  
**PD** = 20 weeks.

**Supervision:** No.  
**Support for behaviour:** NO  
**Specialist:** NA.

**Behaviour:** Exe = VO<sub>2</sub>max (submaximal exercise test).

**Fatigue:** Fatigue severity in 5 domains; mental, motivation, activity, physical, general (MFI), and global fatigue (VAS-100).

**Assessments:** Baseline, 20 weeks, and 52 weeks.

1. **Exe.**

- **Significant** increase in VO<sub>2</sub>max in IG group, which was significantly different from CG.

2. **Significant** decrease in physical fatigue and mental fatigue at 20 weeks in IG, which was significantly different from CG. Significant decrease in physical fatigue at 52 weeks in IG, but no change in CG or significant difference between IG and CG.

(Pukšić et al., 2021)  
Croatia  
RCT

**Focus:** Exe

**IG:** Group yoga programme.

**CG:** Weekly lectures on arthritis related topics.

(Ambrosino et al., 2020)  
Italy  
RCT

**Focus:** Exe

**IG:** home-based movement-based Wii-Fit programme.

**CG:** maintain habitual activity.

**IG:** n = 30,  
100% female,  
age 53 yr,  
disease duration  
7 yr.

**CG:** n = 27,  
89% female,  
age 58 yr,  
disease duration  
9 yr.

**IG:** n = 20, 65%  
female, age 27  
yr.  
**CG:** n = 20,  
60% female,  
age 28 yr.

**SD** = 90 minutes.  
**Int** = Not stated.  
**Freq** = 2 days/week.  
**PD** = 12 weeks.

**Supervision:** Yes.  
**Support for behaviour:** No.  
**Specialist:** Yoga instructor.

**SD** = 50 minutes.  
**Int** = Not stated.  
**Freq** = Daily.  
**PD** = 8 weeks.

**Supervision:** NO.  
**Support for behaviour:** No.  
**Specialist:** NA.

Both **IG** and **CG** completed 4-week comprehensive in-patient rehabilitation programme, including strengthening and aerobic exercise at moderate-to-high intensity, daily 30-minute walk, and movement-based Nintendo Wii-Fit system.

**Behaviour:** Exe = intervention allocation.

**Fatigue:** Fatigue severity (Functional Assessment of Chronic Illness Therapy (FACIT) scale)

**Assessments:** Baseline, 12 weeks, and 24 weeks

**Behaviour:** Exe = intervention allocation.

**Fatigue:** Fatigue severity (FACIT scale)

**Assessments:** Baseline, 4 weeks, 12 weeks.

**1. Exe.**

- Exe assessed based on group allocation.

**2. Significant** difference in fatigue between IG and CG at 12 weeks, but not at 24 weeks.

**1. Exe.**

- Exe assessed based on group allocation.

**2. Significant** improvement in fatigue in IG compared with CG at 8 following time.

(Van Zanten et al., 2021)  
United Kingdom  
RCT

**Focus:** Exe

**IG:** Self-determination theory-based psychological intervention to support behaviour change + aerobic and resistance training exercise intervention.

**CG:** Aerobic and resistance training exercise intervention.

**IG:** n = 43, 63% female, age 55 yr, median disease duration 6 yr.

**CG:** n = 45, 69% female, age 55 yr, median disease duration 5 yr.

**IG: SD** = 60 minutes.  
**Int** = 60-75% of HR max.  
**Freq** = 3 days/week.  
**PD** = 12 weeks.

**PA target** = Not stated.

**Supervision:** No.  
**Support for behaviour:** 2 Faces to face counselling sessions, 3 phone consultations.  
**Specialist:** Behaviour change counsellor.

**CG: SD** = 60 minutes.  
**Int** = 60-75% of HR max.  
**Freq** = 3 days/week.  
**PD** = 12 weeks.

**PA target** = Not stated.

**Supervision:** No.  
**Support for behaviour:** NO.  
**Specialist:** NA.

**Behaviour:** Exe =

- VO2max (exercise tolerance test).
- PA = moderate to vigorous PA (mins/week, IPAQ).

**Fatigue:** Fatigue severity (MAF scale).

**Assessments:** Baseline, 13 weeks, 26 weeks, and 52 weeks.

**1. Exe**

- **No significant** change in Exe or PA in IG.

**2. No significant** change in fatigue in IG.

(Nordgren et al., 2015)  
Sweden  
Intervention

**Focus:** Exe and PA

**IG:** Aerobic and resistance Exe and PA programme combined with support group meetings.

**IG:** n = 220,  
81% female,  
age 59 yr,  
disease duration  
12 yr.

**Exe:**  
**SD** = 45 minutes.  
**Int** = 50% - 80% of 1 rep max & 60%-  
85% of HR max.  
**Freq** = 2 days/week.

**PA target:** >30 minutes moderate  
intensity PA on most days.

**Support group meetings:** Biweekly  
behaviour change supported grounded in  
Social Cognitive Theory.

**PD** = 48 weeks.

**Supervision:** No.

**Support for behaviour:** Yes.

**Specialist:** Physiotherapist.

**Behaviour(s):** Exe =

- Adherence to training programme (weekly self-report, >50% classed as adhering).
- VO2max (submaximal exercise test).
- Grip strength.
- PA = adherence to programme recommendations (adapted from Exercise Stage Assessment instrument – 'are you physically active: 30 minutes moderate intensity aerobic Exe at least 5 days/week and resistance Exe at least 2 days/week).

**Fatigue:** Fatigue severity (VAS-100).

**Assessments:** Baseline and 48 weeks.

**1. Exe and PA**

- **Significant** improvement in VO2max.
- **Significant** improvement in grip strength.

**2. No significant** improvement in fatigue.

Adherence to Exe, PA or group meetings not associated with changes in fatigue.

(Mayoux-Benhamou et al., 2008)

France  
RCT

**Focus:** Exe and PA

**IG:** Education programme including group sessions related to different aspects of PA (e.g., benefits, behaviour change techniques to include PA in daily living, joint protection), practice of home-based exercise, and classes on aquatic and relaxation training + home-based exercise (range of motion, resistance Exe).

**CG:** Usual care + booklet with home-based Exe programme and PA recommendations.

**IG:** n = 104,  
90% female,  
age 55 yr,  
disease  
duration 12  
yr.

**CG:** n = 104,  
89 % female,  
age 54 yr,  
disease  
duration 14  
yr.

**Programme delivery:** 8 weekly 5-hr group sessions.

**Exe targets:** at least exercises each day.

**PA targets:** not stated (compliance quantified as increase in PA of >20% baseline PA levels).

**Supervision:** No.

**Support for behaviour:** Yes.

**Specialist:** Health professional, Physician, occupational therapist, and physical therapist.

**Behaviour(s):** Exe =

- Compliance with Exe programme (at least 3 exercises daily).
- PA = self-reported leisure time PA (Baecke questionnaire, compliance >20% increase in PA at follow up relative to baseline).

**Fatigue:** fatigue severity (FACIT scale).

**Assessments:** Baseline (PA and Fatigue), 26 weeks (Exe, PA, and Fatigue), and 52 weeks (Exe and PA).

## 1. Exe and PA.

- **Significant** higher compliance with home-based Exe in IG compared to CG at 6 months, but not at 12 months.
- **Significant** increase in PA in IG, but not CG at 6 months, but not at 12 months.

- ## 2. No significant difference in changes in fatigue at 6 months between those who complied with home-based Exe (n=13) and those who did not (n=167).

**Significantly** greater decrease in fatigue in those who complied with PA recommendations at 6 months (n=36) and those who did not (n= 136).

(Feldthussen et al., 2016)  
Sweden  
RCT

**Focus:** PA

**IG:** Individual education session related to enhancing PA and balancing life activities for RA (e.g., To devise a mutually agreed self-care plan for managing fatigue) + individual sessions using recommendations for enhancing PA).

**CG:** Usual health care (e.g., usual physical, social activities, pharmacologic treatment and other treatments associated with care).

**IG:** n = 36,  
88% female,  
age 54 yr.

**CG:** n = 34,  
88% female,  
age 52 yr.

**Programme delivery:** Individual education sessions and follow up phone calls– number based on participant preference (median number of in person session 3, duration 30-60 mins, median number of phone calls 1, duration 10-30 mins).

**PA target:** personalised targets, but reference made to PA recommendations (5 days/week of >30 mins moderate PA or 2 days/week >20 mins vigorous PA).

**PD** = 12 weeks.

**Supervision:** No.

**Support for behaviour:** No.

**Specialist:** Physical therapist.

**Behaviour:** PA = leisure-time PA (hrs during previous week Leisure Time Physical Activity Index).

**Fatigue:** General fatigue (VAS-100) and Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire (BRAFM-DQ).

**Assessments:** Baseline, 12 weeks, and 26 weeks.

**1. PA.**

- **Significant** increase in PA in IG at 12 weeks and 6 months, but no change in CG.

**2. Significant** greater decrease in fatigue in IG compared with CG at 12 weeks.

Decrease in fatigue was marginally greater in IG compared to CG at 6 months (p=.057).

(Knittle et al., 2015)

Netherlands

RCT

**Focus:** PA

**IG:** Group educational session related to PA for RA (e.g., benefits, recommendations) + individual sessions using different behaviour change techniques (e.g., goal setting, monitoring behaviour, education, action planning) to support PA.

**CG:** Group educational session related to PA for RA (e.g., benefits, recommendations).

**IG:** n = 38, 79% female, age 61 yr.

**CG:** n = 40, 55% female, age 65 y.

**Programme delivery:** One group educational session, 3 face-to-face individual session (40-60 minutes), 3 follow up phone calls.

**PA target:** Increase in duration, frequency, and intensity of PA.

PD = 6 weeks.

**Supervision:** No.

**Support for behaviour:** 2 Faces to face counselling session, 1 phone consultation.

**Specialist:** Physiotherapist, rheumatology nurse.

**Behaviour:** PA = leisure-time PA, days per week with >30 mins of PA (Short Questionnaire to Assess Health-enhancing physical activity, SQUASH questionnaire).

**Fatigue:** Fatigue severity (CIS-20).

**Assessments:** Baseline, 6 weeks, and 32 weeks.

**1. PA.**

- **Significant** increase in leisure time PA and days per week with 30 mins of PA in IG compared to CG (significant interaction effect).

**2. No significant** changes in fatigue in either IG or CG.

(Katz et al., 2018)

United States of America  
RCT

**Focus:** PA

**IG1:** Educational booklet and guided discussion on how to increase PA + pedometer and diary to record daily steps.

**IG2:** Educational booklet and guided discussion on how to increase PA + pedometer and diary to record daily steps + individualised step targets.

**CG:** educational booklet and guided discussion on how to increase PA.

**IG1:** n = 34,  
88% female,  
age 56 yr,  
disease  
duration 12  
yr.

**ICG2:** n = 34,  
88% female,  
disease  
duration 13  
yr.

**CG:** n = 28,  
86% female,  
age 59yr,  
disease  
duration 21  
yr.

**IG1: Programme delivery:** educational booklet and discussion and instructions about pedometer.

**PA target:** Not stated.

**PD** = 20 weeks.

**Supervision:** No.

**Support for behaviour:** No.

**Specialist:** Not stated.

**IG2: Programme delivery:** educational booklet, discussion and instructions about pedometer, daily step targets.

**PA target:** Every 2 weeks, increase daily step counts by 10%.

**PD** = 20 weeks.

**Supervision:** No.

**Support for behaviour:** NO.

**Specialist:** Not stated.

**Behaviour:** PA = weekly average number of daily steps (Jawbone Up pedometer).

**Fatigue:** Fatigue severity (PROMIS fatigue short form).

**Assessments:** Baseline, week 10 (fatigue only), week 21.

**1. PA.**

- **Significant** increase in PA in IG1 and IG2, but not CG. Increased in IG1 and IG2 greater than changes in CG. Greater weekly increase in daily steps in IG2 compared to IG1.

**2. Significant** decrease in fatigue at 10 weeks and 21 weeks in IG1 and IG2, but not CG.

(Li et al., 2020)

Canada  
RCT

**Focus:** PA

**IG:** PA programme including behavioural support and activity monitor.

**CG:** waiting-list control group receiving monthly arthritis news unrelated to PA via email.

**IG:** n = 43,  
88% female,  
age 55 yr.

**CG:** n = 43,  
93% female,  
age 55 yr.

**Programme delivery:** One group and individual counselling session and biweekly phone calls.

**PA:** Provision of activity monitor (Fitbit Flex 2) and software to monitor PA.

**PA targets:** individualised based on counselling session.

**SB targets:** Individualised based on counselling session.

**PD = 8 weeks.**

**Supervision:** No.

**Support for behaviour:** Face to face counselling session and telephone calls.

**Specialist:** Physiotherapist.

**Behaviour:** PA = objective light and moderate to vigorous PA (min/day; SB = sedentary time (min/day) – both FitBit Flex 2 activity monitor.

**Fatigue:** Fatigue severity (Fatigue Severity Scale).

**Assessment:** Baseline and 9 weeks.

**1. PA and SB.**

- **Significantly** greater improvement in moderate to vigorous PA in IG compared to CG.

- **No significant** changes in SB.

**2. No significant** changes in fatigue.

(Thomsen et al., 2017)  
Denmark  
RCT

**Focus:** SB

**IG:** Individually tailored behavioural intervention to increase light PA by reducing sitting time.

**CG:** Continue usual lifestyle.

**IG:** n =75, 81% female, age 60 yr, disease duration 12 yr.

**CG:** n = 75, 80% female, age 60 yr, disease duration 11 yr.

**Programme delivery:** 60-90 minutes individual motivational counselling sessions focussed on education, goal setting, and self-efficacy.

Weekly SMS reminders related to individual goals (frequency agreed by participant).

**Intervention targets:** Reduce daily TV viewing, substitute standing where possible, break up prolonged sitting, maximum 30 minutes of sitting per episode.

**Supervision:** No.

**Support for behaviour:** Face to face counselling session, SMS/text message.

**Specialist:** Nurse or occupational therapist.

**Behaviour:** SB = daily sitting time (hours/day, ActivPAL), PA = daily stepping time (hours/day, ActivPAL).

**Fatigue:** Fatigue severity in 5 domains; mental, motivation, activity, physical, general (MFI), and fatigue severity (VAS-10).

**Assessment:** Baseline and 16 weeks.

**1. SB.**

- **Significant** greater decrease in daily sitting time in IC compared to CG.

- **Significant** greater increase in daily steps in IG compared to CG.

**2. Significant** greater improvements in all fatigue measures in IG compared to CG.

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**Note:** **RCT** = Randomised Controlled Trial, **IG** = Intervention Group, **CG** = Control Group, **Exe** = Exercise, **PA** = Physical Activity, **SB** = Sedentary Behaviour, **SD** = Session Duration, **Int** = Intensity, **Freq** = Frequency, **PD** = Programme Duration, **HR** = Heart Rate, **MAF** = Multidimensional Assessment of Fatigue, **MFI** = Multidimensional Fatigue Inventory. **VAS** = Visual Analogue Scale. **FACIT** = Functional Assessment of Chronic Illness Therapy-fatigue scale, **POMS** = Profile of Moods Scale, **PROMIS** = Patient-Reported Outcome Measurement Information System.

**CHAPTER3: DIURNAL PATTERNS OF PHYSICAL ACTIVITY AND  
SEDENTARY BEHAVIOUR ON FATIGUE IN RHEUMATOID ARTHRITIS: A  
CROSS- SECTIONAL STUDY**

## Introduction

**Rheumatoid arthritis (RA)** is a chronic inflammatory disease affecting 0.5–1% of the adult population, and is characterised by inflammation and deformation of the synovial joints, resulting in reduced mobility and physical function (Lee et al., 2012). **Fatigue** is also a common symptom of RA, with most people living with RA reporting that they suffer from fatigue on most days (Metsios and Kitas, 2018). It is considered by patients to be one of the most unmanageable symptoms of RA, and research into fatigue management is consistently ranked as a top priority by patients and healthcare professionals (lfesemen et al., 2022; Kirwan et al., 2007). Fatigue in RA is complex; the experience of fatigue can have a physical, cognitive, emotional, and social impact, which, in combination with the fluctuations within and between days has been increasingly acknowledged to influence daily life (Dures et al., 2023; Primdahl et al., 2019). Fatigue can be measured using several standardised questionnaires but is frequently measured using tools such as visual analogue scales (VAS) and numerical rating scales (NRS). However, these questionnaires are simple unidimensional scales that primarily focus on measuring fatigue intensity, and do not capture the different dimensions of fatigue or the perceived impact of fatigue.

The multidimensional fatigue inventory (MFI-20) (Smets et al., 1995) is a validated questionnaire that assesses these different aspects of fatigue. More specifically, it measures general fatigue (reflecting overall sense of fatigue), physical fatigue (physical sensations of fatigue), mental fatigue (mental sensations, such as cognitive fog or mental drain), as well as reduced activity

(impact of fatigue on doing usual activities or tasks) and reduced motivation (lower willingness to do activities). Therefore, this provides a detailed measure of both the different dimensions of fatigue and its impact in everyday activities, and has been frequently used to explore the effectiveness of interventions on levels of fatigue in RA ([Farisogullari et al., 2023](#); [Santos et al., 2023](#)).

A number of observational studies report higher levels of engagement in PA is associated with lower levels of fatigue in RA ([Katz et al., 2016](#); [Mancuso et al., 2006](#); [Reinseth et al., 2011](#); [Rongen-van Dartel et al., 2014](#)). In addition, several randomised controlled trials successful at increasing PA in RA, have reported improvements in fatigue ([Feldthusen et al., 2016](#); [Katz et al., 2018](#)). In addition, systematic review with meta-analysis found that physical activity and exercise interventions have an impact on fatigue ([Cramp et al., 2013](#); [Santos et al., 2023](#)). Given the increasing evidence for the benefits of PA for reductions in fatigue in RA ([Santos et al., 2023](#)). PA is now included as a recommendation for fatigue management in people with inflammatory rheumatic and musculoskeletal disease ([Dures et al., 2023](#)). However, PA is only part of the movement continuum, with the remainder of the waking day comprised of sedentary time. With this in mind, it is important to consider the role of these behaviours on fatigue in RA too.

Sedentary behaviour (SB) is defined as any waking behaviour characterised by energy expenditure of  $\leq 1.5$  metabolic equivalents and a sedentary or supine posture (e.g., watching television, computer use, reading and driving) ([Behaviour, 2012](#)). The functional limitations associated with RA mean people living with this disease are at increased risk of leading a sedentary lifestyle.

Several studies exist which report on the potentially negative consequences of

'sedentary behaviour' among RA patients (Fenton et al., 2020). In two previous cross-sectional studies, positive associations were found between sedentary behaviour and fatigue in RA (Brady et al., 2021; Løppenthin et al., 2015). A previous longitudinal study also reported a significant positive bidirectional relationship between sedentary behaviour and fatigue in RA (O'Brien et al., 2021). The possible benefits of reducing sedentary behaviour for people living with RA were also highlighted by a randomised controlled trial which reported concurrent reductions in sedentary behaviour and improvements in fatigue in this patient group (Thomsen et al., 2017).

Whilst evidence is accumulating for the role of PA and sedentary behaviour for fatigue in RA, most research has relied on estimates of habitual (daily) PA and sedentary behaviour to explore these associations (e.g. minutes/day). Using only aggregate measures of PA and sedentary time recorded over several days, obscures the temporal patterns of this behaviour. An understanding of diurnal variations in PA and sedentary time will give insight into movement patterns in RA, which is critical to the development of interventions. Indeed, factors related to the chronobiology of RA (e.g. morning stiffness) may influence daily patterns of PA and sedentary time in particular ways, which could be used to inform the timing of interventions focussed on these behaviours (e.g., targeting periods of low PA and high sedentary time). Exploring associations between daily patterns of PA and sedentary time accumulation and fatigue in RA, will also provide valuable insight into the potential effects of interventions targeting specific "low PA and/or high sedentary" windows of time.

The aim of this study is therefore to (1) examine diurnal patterns of PA and sedentary behaviour in people living with RA and (2) examine whether these

diurnal patterns of PA and sedentary behaviour are associated with different aspects of fatigue in these patients.

## **Methods**

This study presents secondary analysis of an existing study for which the complete protocol and methods have been previously published ([O'Brien et al., 2021](#)). Below, we highlight aspects of the protocol that are relevant to answer the research question posed in this study.

### ***Participants***

Patients with RA (n = 104) were recruited from outpatient clinics at Russells Hall Hospital (Dudley, United Kingdom). Inclusion criteria were a clinical diagnosis according to ACR/EULAR classification criteria ([Aletaha et al., 2010](#)) and an age of  $\geq 18$  years. Patients who were pregnant, used a wheelchair and/or were unable to ambulate independently (including with the assistance of a walking aid/device) were excluded. All patients gave written informed consent to participate prior to undertaking any study procedures. This study was approved by the West Midlands National Health Service Research Ethics Committee (16/WM /0371).

### ***Protocol***

Participants attended the hospital on two occasions, one week apart. During the first visit, participants medical history and demographic information was recorded. Following which they underwent a series of assessments to characterise their physical health and RA disease severity. Participants were then provided with an activPAL device to wear for the subsequent 7-days, to

measure sedentary, standing, and stepping behaviours. During the second visit, participants returned the activPAL device, underwent an assessment of their RA disease activity, and completed a questionnaire asking about their experience of fatigue over the last two weeks.

## **Measures**

### ***Medical history and demographic information***

Participants provided self-reported information about their age, gender, ethnicity, marital status, date of diagnosis, existing chronic conditions, and current medications.

### ***Physical health assessments***

Height and weight were measured to the nearest 0.1 m (SECA, Leicester Height Measure) and 0.1kg (Tanita BC-418 MA P), respectively. Resting systolic and diastolic blood pressure was measured using an automatic blood pressure monitor (Mindray Accutorr PLUS).

### ***RA disease severity***

RA disease severity was assessed using the Stanford Health Assessment Questionnaire (Fries et al., 1980). The HAQ assesses participants' physical function by recording their ability to perform activities of daily living (ADLs), and has been validated for use in people living with RA and (Fries et al., 1980). The ADLs are divided into eight sections: 'dressing and grooming', 'getting up', 'eating', 'walking', 'hygiene', 'reaching', 'grasping' and 'activities'. Participants rated how difficult it was to perform specific tasks related to each ADL over the past two weeks on a scale from 0 (no difficulty) to (not possible). Average

scores for physical function were calculated, with higher scores representing poorer physical function. The HAQ showed high internal reliability in this study  $\alpha=.81$ .

### ***RA disease activity***

The Disease Activity Score-28 (DAS-28) was used to measure RA disease activity (Prevoo et al., 1995). DAS-28 is determined by evaluating the number of swollen and tender joints across 28 specific joints in the body (including the hands, wrists, elbows, shoulders, and knees), in conjunction with a patient's Erythrocyte Sedimentation Rate (ESR) and their self-reported overall health. Self-reported overall health is reported on a visual analogue scale from 0 (very good) to 100 (very poor).

### ***Fatigue***

Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20) (Smets et al., 1995). The MFI-20 consists of 20 items that measure the severity of fatigue related to five fatigue domains: general fatigue, mental fatigue, physical fatigue, reduced activity, and reduced motivation. Participants are asked to respond to 20 statements (4 per domain) indicating the extent to which the statement is true for them, on a scale of 1 (Yes, that is true) to 5 (No, that is not true). Example statements include, "I feel tired" (general fatigue), "Physically I feel I am in a bad condition" (physical fatigue), "It takes a lot of effort for me to concentrate on things" (mental fatigue), "I am get little done" (reduced activity), and "I don't feel like doing anything" (reduced motivation). The final scores for each of the MFI domains can range from 4 to 20, with higher scores indicating higher levels of fatigue for that domain. The MFI has been validated for use in

RA (Goodchild et al., 2008; Rupp et al., 2004). In this study, the MFI showed high internal reliability (general:  $\alpha=.79$ : physical:  $\alpha=.78$ : mental:  $\alpha=.81$ : reduced activity:  $\alpha=.79$ : reduced motivation:  $\alpha=.79$ ).

### ***Sedentary time and physical activity***

Sedentary time and PA (standing and stepping) were measured using the ActivPAL3™ (PAL Technologies Ltd, Glasgow, UK). This device is considered the gold standard for measuring free-living sedentary time (Chastin et al., 2018) and has been validated for measuring free-living sitting, standing and stepping time in people living with RA (O'Brien et al., 2020). Participants wore the ActivPAL3™ for 7-days, over continuous 24-hour periods. The device was attached to mid-anterior position of the participants right thigh using a waterproof adhesive dressing. Proprietary software was used to set-up the devices to record movement data in 15-second epochs (PAL Connect, PAL Technologies Ltd, Glasgow, UK). After 7-days, devices were returned to the research team, and data were downloaded into Microsoft Excel for analysis.

### ***ActivPAL™ data reduction***

In Microsoft Excel, the researcher manually reviewed the activPAL3 data to identify sleep vs. wake periods. Sleep periods were identified as consecutive zero counts  $\geq 60$  minutes between the hours of 9pm and 9am. Where zero counts were interrupted with periods of movement  $\geq 2$  minutes, then the sleep period was considered to end, and the wake period to begin. Sleep periods were subsequently removed from the data and were not included in daily activity time estimates. To be included in the data analyses, participants had to wear the activPAL3 for at least 10 hours a day, at least 5 days a week.

Subsequently, for participants with valid data, activPAL data representing participants awake time were examined hourly from 7:00 to 22:59 to identify specific hours of non-wear. Days were split into specific time segments: morning – 7:00 to 11.59, afternoon – 12:00 to 17.59, and evening – 18:00 to 22.59. Within the defined morning, afternoon and evening time periods, minutes spent sedentary, standing and stepping as well as stepping intensity were averaged over the respective hours. For example, to determine afternoon sedentary time, the minutes of sedentary time recorded within each hour (e.g. 12:00 to 12:59, 13:00 to 13:59, 14:00 to 14:59, 15:00 to 15:59, 16:00 to 16:59, and 17:00 to 17:59) were summed and divided by six. Time periods that were based on only 1 hour of valid wear time were excluded from further analyses. Next, the time values of the individual days were averaged to calculate an overall morning, afternoon, and evening value per participant for sitting, standing, stepping, and step intensity. For three participants, the mean value was based on data from five days, for the remaining participants, the data was based on data for six days. Out of those, four participants only had morning data available for five days, but afternoon and evening data for six days. One participant was excluded from analyses as valid day for the morning time period was only available for one day. The final sample for analyses contained 100 participants. This approach of dividing the day into morning, afternoon and evening segments to examine daily movement patterns, is consistent with methods used in previous research examining diurnal patterns of sedentary time and PA in individuals with RA ([Fenton et al., 2020](#)).

### **Statistical analysis:**

First, mixed linear modelling was used to explore changes during the day in sedentary, standing, and stepping time as well as step intensity, given that this approach does not assume sphericity of the data, can process non-normally distributed data and deal with occasional missing data (Hoffman, 2015). The within-subject level predictor was Time (centered by assigning 0 to morning), with sex (female = 0), mean centered age, disease activity (DAS28), and disease severity were entered as level 2 (between-person) covariates.

Subsequently, the mean centered fatigue was added to this model as a between-person predictor, with each fatigue outcome (general fatigue, mental fatigue, physical fatigue, reduced activity, reduced motivation) analyzed separately. Potential differences in diurnal patterns with varying levels of fatigue were explored using mean-centered fatigue by time interactions. It is worth noting that fatigue by time interaction reflects whether the rate of change from morning to either afternoon or evening is similar for varying levels of fatigue for a female of average age, disease severity, and activity.

## Results:

**Table 3.1:** Participant characteristics

	<i>Mean ± SD n= 100</i>	<i>Range (min-max)</i>
<b>Demographics</b>		
<i>Age (Years)</i>	58 ± 12	26 – 80
<i>Gender (% Women)</i>	70	-
<i>Ethnicity (%)</i>	Caucasian 95	-
	Asian Indian 2	
	Black Caribbean 2	
	Arab 1	
<b>RA features</b>		
<i>Disease duration (Years)</i>	10 ± 10	1 – 52
<i>Disease activity (DAS28)</i>	4 ± 1.5	0.49 – 7.20
<i>Disease severity (HOQ)</i>	1.3 ± 0.8	0.00 – 2.88
<i>Medication</i>		
<i>DMARDS (%)</i>	90	-
<i>Anti-TNF (%)</i>	14	-
<i>NSAIDS (%)</i>	19	-
<b>Fatigue outcomes (MFI-20)</b>		
<i>General fatigue</i>	13 ± 4	4 – 20
<i>Physical fatigue</i>	13 ± 4	4 – 20
<i>Mental fatigue</i>	10 ± 4	4 – 17
<i>Reduced activity</i>	11 ± 4	4 – 20
<i>Reduced motivation</i>	10 ± 4	4 – 20

Note: **DAS28** = Disease Activity Score-28, **HOQ** = Health Assessment Questionnaire, **(MFI-20)** = Multidimensional Fatigue Inventory.

### **Participant characteristics**

**Table 3.1** describes the study participants. The majority of participants were female and Caucasian. On average, participants had a disease duration of 10 years, moderate disease activity and low to moderate disability. The majority of participants were taking a mix of medications, with the majority on DMARDS. The mean scores for the fatigue subscales showed overall moderate levels of fatigue, but with substantial variability between participants.

### ***Diurnal patterns in movement behaviours:***

**Table 3.2:** Estimated means for time spent sedentary, standing, stepping and step intensity during the morning, afternoon, and evening periods.

<b><i>Time of day</i></b>	<b><i>Sitting (mins/hr)</i></b>	<b><i>Standing (mins/hr)</i></b>	<b><i>Stepping (mins/hr)</i></b>	<b><i>Step intensity. (number/hr)</i></b>
<i>Morning</i>	30.95	21.27	7.78	596.79
<i>Afternoon</i>	31.94	20.31	7.75	593.47
<i>Evening</i>	43.35*	12.43*	4.23*	306.21*

Note \*Significantly different from morning and afternoon,  $p < .05$ ; Values are min/hour (for sitting, standing, and stepping) and number/hour (for step intensity). Data represent the estimated mean for females with average age, disease activity (DAS28) and (HOQ) disease severity.

The average time spent sitting, standing, and stepping per hour throughout the day is reported in **Table 3.2**, along with the average step intensity during each period of the day. Results suggests sitting time is significantly higher, and standing time is significantly lower, in the evening compared to the morning and afternoon. Stepping time and step intensity are similar in the morning and the afternoon and are significantly lower in the evening compared to both of these time periods.

Associations between movement behaviours and age, sex, DAS28 (disease activity) and HAQ (disease severity) scores were also examined. No associations were observed for age or HAQ. However, results demonstrated a significant effect of sex on all behaviours, with females sitting less, but standing and stepping more than males. Females also demonstrated a higher step intensity than males. There was also a significant positive association between DAS28 scores and sitting, suggesting participants with a higher disease activity spent more time sedentary.

**Sitting:** Minutes of sitting per hour were significantly positively associated with fatigue dimensions reduced activity [EM = 0.57,  $p = .013$ ], and reduced motivation [EM = 0.45,  $p = .046$ ], suggesting that participants with higher levels of sitting reported higher fatigue in these domains. No such associations were found for general fatigue [EM = 0.19,  $p = .394$ ], physical fatigue [EM = 0.43,  $p = .079$ ], or mental fatigue [EM = 0.14,  $p = .531$ ] outcomes. In addition, no significant interaction effects were found between diurnal patterns of sitting with any fatigue outcome. Interestingly, the significant positive association between DAS28 and sitting that was observed in the model without fatigue, was no longer significant when general fatigue and mental fatigue were included in the model.

**Standing:** Standing time per hour was significantly negatively associated with the fatigue dimension of reduced activity [EM = -0.42,  $p = .029$ ], suggesting participants who spent more time standing, reported lower levels of this fatigue outcome. No such associations were found for general fatigue [EM = -0.04,  $p = .843$ ], physical fatigue [EM = -0.18,  $p = .379$ ], mental fatigue [EM = -0.09,  $p = .637$ ] or reduced motivation [EM = -0.29,  $p = .118$ ] outcomes. No significant interaction effects were found between diurnal patterns in standing with any fatigue domain.

**Stepping:** Minutes of stepping per hour were significantly negatively related to general fatigue [EM = -0.15,  $p = .038$ ], physical fatigue [EM = -0.25,  $p = .002$ ], reduced activity [EM = -0.16,  $p = .044$ ] and reduced motivation [EM = -0.16,  $p = .038$ ] outcomes. This suggests participants with higher levels of stepping reported lower levels of general, physical, reduced activity and reduced motivation fatigue outcomes. No such associations were found for mental

fatigue [EM = -0.06,  $p = .472$ ]). Significant interaction effects were found between stepping behaviour and some fatigue outcomes, whereby stepping in the evening was positively associated with general fatigue [EM = 0.18,  $p = .019$ ) and physical fatigue [EM = 0.15,  $p = .038$ ]). This suggests participants who experience overall higher levels of general and physical fatigue decrease their time spent stepping in the evening to a lesser extent, compared to those who have lower levels of general and physical fatigue.

**Step intensity:** Step intensity per hour was significantly negatively associated with fatigue domains of; general fatigue [EM = -17.5,  $p = .008$ ], physical fatigue [EM = -26.5,  $p = .001$ ], reduced activity [EM = -14.7,  $p = .035$ ] and reduced motivation [EM = -13.9,  $p = .043$ ]. This suggests that participants who engaged in steps at at higher intensity, reported significantly lower levels of fatigue in these domains. No associations were found between step intensity and mental fatigue [EM = -6.5,  $p = .347$ ]. Significant positive interaction effects were found between step intensity in the evening, with general fatigue [EM = 19.3,  $p = .004$ ], physical fatigue [EM = 17.1,  $p = .007$ ] and reduced motivation [EM = 14.1,  $p = .049$ ]). This suggests participants who experience higher levels of general fatigue, physical fatigue and reduced motivation, decrease the stepping at a higher intensity during the evening to a lesser extent, compared to those who have lower levels of general fatigue, physical fatigue, or reduced motivation.

## **Discussion**

**Description the result** (Describe associations between behaviours and fatigue measures overall)

This study examined the associations between movement behaviours measured by the activPAL™ (sitting, standing, stepping and step intensity), with diurnal patterns of fatigue among people living with RA. Results suggest that in the evening (between 18:00 and 22:59), people living with RA tend to sit more, stand less, and engage in fewer steps, compared to the morning and the afternoon. In addition, step intensity is lower in the evening compared to earlier periods of the day. Regarding associations between diurnal movement patterns and fatigue outcomes, results indicate that movement behaviours are differentially associated with dimensions of fatigue. Specifically, time spent sitting and standing demonstrated fewer associations with fatigue outcomes, compared to stepping behaviours. In addition, whilst all behaviours were associated with the reduced activity dimensions of fatigue, only stepping behaviours were associated with general and physical fatigue dimensions. There was no notable connection between diurnal patterns of sitting or standing with fatigue outcomes. However, significant interactions were observed for stepping behaviours, whereby general and physical fatigue were related to the reduction in evening steps (both min/hour and steps/hour [intensity]) and reduced motivation to step intensity in the evening.

### ***Comparisons with other studies and compare other studies***

To our knowledge, this is the first study to examine how diurnal patterns in movement behaviours are associated with different dimensions of fatigue in RA. Previous studies have largely concentrated on exploring associations between overall daily levels of sedentary time and/or physical activity with total levels of fatigue ([Brady et al., 2021](#); [Løppenthin et al., 2015](#); [O'Leary et al., 2020](#); [O'Brien](#)

et al., 2021). The approach adopted in this study will enable a more detailed understanding of how variations movement behaviours throughout the day may be related to different facets of fatigue. A recent study adopted a similar methodology, and examined differences in levels of accelerometer-assessed sedentary time, light- and moderate-to-vigorous intensity physical activity in the morning, afternoon and evening in people with RA (Fenton et al., 2020). This study reported similar findings to those observed here, whereby sedentary time was higher, and light- and moderate-to-vigorous intensity physical activity was lower in the evening, compared to the morning and afternoon. Sedentary time estimates in the prior study were slightly higher (~5-7 minutes) during all time periods of the day, which may be due to differences in methods used to assess sedentary time. Fenton et al., 2020 employed accelerometers, which may misclassify stationary physical activity (i.e. standing), as sedentary time (Fenton et al., 2020). The activPAL employed in this study demonstrates superior validity and reliability compared to accelerometers, and has been validated for measurement of sedentary time in RA, reporting >99% classification accuracy for both measurement of sedentary and standing time (O'Brien et al., 2020).

In examining associations between sedentary behaviour and fatigue dimensions, our results showed sedentary time was only significantly positively associated with reduced activity and reduced motivation. This is in contrast to previous research, which has shown positive associations between sedentary time with all MFI fatigue dimensions. For example, two studies have reported significantly positive associations between overall self-reported daily sedentary time and physical fatigue in RA (Brady et al., 2021; Løppenthin et al., 2013). The reason for the differences in these associations could be due to the self-

reported nature of sedentary behaviour in previous studies. Still, an intervention study aiming to reduce sedentary time in RA reported decreases in activPAL-assessed sedentary time among in the intervention group, in parallel to decreases in all dimensions of fatigue (general, physical, mental, reduced activity, and reduced motivation) (Thomsen et al., 2017). However, the extent to which reductions in sedentary time per se were responsible for the decreases in fatigue is not clear, as significant increases in standing and stepping time were also observed in the intervention group pre to post intervention.

Concerning the relationship between standing and fatigue dimensions, our results revealed standing was only associated with the outcome of reduced activity. Two previous studies have reported a negative association between standing time with fatigue overall in people living with RA. However, no studies to date have specifically explored the association between standing time and different dimensions of fatigue (O'Leary et al., 2020; O'Brien et al., 2021). This may be because standing time is a relatively novel concept in RA research, which emerged to align with thinking that promoting physical activity in RA may require a progressive “step change”, whereby sedentary time could be replaced with standing as a form of light-intensity physical activity (O'Brien et al., 2021; Thomsen et al., 2017). As such only a few existing studies have employed the activPAL as a measure of standing in RA, and more research is required to understand the role of standing for all RA outcomes, including fatigue.

Our study found that hourly stepping minutes and step intensity were significantly negatively associated with several dimensions of fatigue; general fatigue, physical fatigue, reduced activities and reduced motivation. Previous cross-sectional studies in have reported significant negative associations

between the number of steps per day with overall fatigue measured by the by the self-reported in a diary daily, using a numerical rating scale (NRS) (Hegarty et al., 2015). In addition, a walking intervention study in RA reported a greater weekly increase in daily steps was associated with decreases in total fatigue assessed with the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue short form (Katz et al., 2018). Our results provide further insight into the associations between stepping behaviour and fatigue, suggesting that both the average daily time spent stepping and average step intensity, may hold implications for multiple dimensions of fatigue.

In addition, the current results elucidating the potential role sitting, standing and stepping behaviours for different dimensions of fatigue, they are also the first to suggest there may be a diurnal factor to consider in these associations.

Specifically, the significant interaction effects suggested that individuals who spent more time stepping in the evening, and stepped at a higher intensity, reported the highest levels of general and physical fatigue. It is interesting that these interactions were observed primarily for general and physical fatigue dimensions, which could suggest that for those individuals that have maintained higher stepping behaviour more consistently throughout the day, the cumulative effect of this sustained activity could heighten their experience of general and physical fatigue. Indeed, average steps per hour and step intensity for the entire sample were both significantly lower in the evening, when compared to the morning and afternoon. Therefore, any individuals above the mean value are likely to be maintain steps closer towards the levels observed in the morning and afternoon.

Surprisingly, we did not find any evidence to suggest that movement behaviours are associated with mental fatigue in this study. This somewhat contradicts prior research, in which a negative association between light physical activity and mental fatigue was observed in individuals with RA ([Brady et al., 2021](#)). In addition, a recent study reported a decrease in mental fatigue measured by the MFI after an intervention in which people with RA engaged in 20 weeks of light home-based exercise combined with gym-based high intensity aerobic and resistance exercise ([Kucharski et al., 2019](#)). It is interesting that both of these studies reported associations with light-intensity activity, which our study did not specifically investigate. It is therefore possible that light-intensity physical activity may be particularly important to consider in the context of fatigue management in RA. In research they found that physical fatigue had an impact, on overall fatigue in the morning compared to mental fatigue and this difference grew to 33% as the day went on. Throughout the day, feeling fatigue earlier was linked to fewer steps taken, less light physical activity, and less time spent standing later. There was a link between mental and feeling fatigue worn out as mental activity resulted in both mental and general fatigue. Conversely experiencing fatigue decreased engagement in activities among individuals, with knee osteoarthritis ([Fawole et al., 2020](#)). On other hand, Research consistently indicates a link, between sedentary behaviour and mental fatigue in individuals with multiple sclerosis (MS). This connection is especially noteworthy in the realm of MS, where fatigue's prevalent and can be disabling. The research emphasises the significance of addressing how individuals perceive and respond to symptoms along, with psychological aspects, when managing fatigue in MS ([Garg et al., 2016](#); [Trojan et al., 2007](#); [Veldhuijzen van](#)

Zanten et al., 2016). Such findings should encourage further investigation regarding the role of different types of physical activity behaviours and their varying effects on mental fatigue, as well as other fatigue dimensions.

### ***Interventions and Evening Sedentary Behaviour***

Taken together, the results of this study have several implications for fatigue management in RA, through supporting more movement. First, our findings suggest that interventions aiming to reducing sedentary time and/or increase standing and stepping, may hold most promise for improving the reduced activity aspects of motivation, as all behaviours were associated with this outcome. Second, interventions which aim to replace sitting with higher intensity stepping specifically, may prove most beneficial for improving the experience of fatigue in RA, as higher step intensity negatively was associated with all fatigue dimensions, except mental fatigue. Third, whilst the lower levels of stepping time and step intensity in the evening may suggest that this is to optimal time to intervene to increase movement (i.e., more room for improvement), the significant, positive interactions observed between evening stepping and some fatigue outcomes may indicate otherwise. Instead, interventions aiming to increasing stepping earlier in the day, and this allowing time for physical rest in the evening, may improve some feelings of fatigue in RA. Still, experimental research which examines how diurnal variations in movement behaviour are associated with changes in fatigue is vital prior to developing interventions and management strategies.

### ***Other factors associated with sitting, standing, stepping***

Our findings showed no associations between disease severity and age, with sitting, standing, or stepping. This is in contrast to several previous studies that have reported associations between sedentary behaviour and physical activity with disease severity ([Fenton et al., 2020](#); [Løppenthin et al., 2015](#); [Rongen-van Dartel et al., 2014](#)). However, findings showed that females spent less time sitting, but had higher levels of standing, stepping, and stepping intensity compared to males. This pattern aligns with similar results from previous research involving older adults, with males spending more time sedentary than females ([Arnardottir et al., 2013](#); [Yerrakalva et al., 2017](#)). Indeed, the relationship between sedentary time and gender in older adults with rheumatoid arthritis is not specifically addressed in the literature. In addition, our study also showed associations between disease activity (DAS-28) and sitting time, but these associations were not present when fatigue was included in statistical models. Together, these findings suggest that gender differences in movement patterns may exist, indicating the need for tailored interventions targeting sedentary behaviour. In addition, such interventions may not need to consider variability in disease activity, as difference between individuals in this respect may not influence the effectiveness of interventions on fatigue outcomes.

### **Strengths and limitations**

Our study provides novel insights into the diurnal patterns of fatigue and movement, contributing to a deeper understanding of these dynamics in RA. The use of activPAL in our study, acknowledged as the gold standard for measurement of free-living sedentary behaviour, enhances the reliability and

accuracy of our findings. Furthermore, we examined various dimensions of fatigue, offering a multidimensional perspective and comprehensive assessment of fatigue, enriching the depth of our analysis. Still, while the MFI used in this study provides valuable information, self-reported fatigue remains subjective and is influenced by factors such as mood and external circumstances ([Hegarty et al., 2015](#); [Katz et al., 2018](#)). Incorporating more objective measures of fatigue would strengthen the reliability of fatigue assessments, although objective markers for fatigue are currently lacking. A further limitation of this study is the cross-sectional. Future studies adopting a longitudinal approach, and employing methods such as Ecological Momentary Assessment (EMA), would provide a more comprehensive understanding of the dynamic associations between movement patterns and fatigue in RA. (EMA) is a method used to collect data, on people's behaviours, emotions, and experiences in their surroundings ([Hoppmann and Ho, 2015](#)). This technique has been utilised in areas like health, education, and studies on depression among adults([Carson et al., 2010](#); [Kampshoff et al., 2019](#); [Kim et al., 2020](#)). According to Stones research in 1997 it was discovered that stressors and poor sleep were linked to increased pain and fatigue in RA patients through EMA ([Stone et al., 1997](#)). However, we couldn't find any studies specifically focusing on the impact of PA and SB on fatigue in RA through EMA. This highlights the need, for research to explore the applications of EMA within the context of RA.

## **Conclusion**

The results of this study suggest that for people living with RA, the evenings are the most sedentary and least active time periods of the day. In addition, movement behaviours are differentially associated with dimensions of fatigue in this patient group, with stepping behaviour demonstrating the most consistent associations across all fatigue dimensions. Interventions which aim to encourage stepping behaviours may offer a valuable approach toward fatigue management in RA stepping, but diurnal patterns of behaviour and associations with fatigue should be considered in intervention design. Prior to intervention, longitudinal research enabling investigation of the dynamic associations between fatigue and movement behaviours in RA are required. Ecological momentary assessment may offer such an opportunity.

**CHAPTER 4: DIURNAL PATTERNS OF PHYSICAL ACTIVITY AND  
SEDENTARY BEHAVIOUR ON FATIGUE IN STUDENT USING  
ECOLOGICAL MOMENTARY ASSESSMENT: A CROSS- SECTIONAL  
STUDY**

## Introduction

Feelings of fatigue are common and have a significant negative impact on mental health and quality of life ([Junghaenel et al., 2011](#)). Fatigue is an extreme state of physical and/or mental exhaustion after normal activities ([Higson-Sweeney et al., 2022](#)), and is a prominent symptom of several mental illnesses, including depression, anxiety and insomnia ([Demyttenaere et al., 2005](#); [Morin and Benca, 2012](#)). Fatigue is not only evident in clinical populations, but also in the general population, and has been reported to be the most common reason for people visiting their GP ([Rosenthal et al., 2008](#); [Sunwoo et al., 2022](#)).

Fatigue is prevalent in the general population, with reports as high as 60% of the general population and an increase in prevalence is seen during adolescence ([Bruce et al., 2017](#); [Herring et al., 2018](#); [Rhee et al., 2005](#)).

Adolescence is therefore a critical period in terms of the development of fatigue, as fatigue prevalent in adolescence is often continued into adulthood ([Sommer et al., 2023](#)). Indeed, high levels of fatigue are observed among university aged students ([Ter Wolbeek et al., 2008](#)). For example, studies suggest 20% of female students report experiencing significant fatigue and this fatigue is sustained over the course of a year in a quarter of these students ([Ter Wolbeek et al., 2006](#)). Fatigue can contribute to poor academic performance and exacerbate other mental health problems, such as stress and anxiety in student populations ([Wilks et al., 2020](#)). Given the prevalence of fatigue and the reported impact of fatigue on quality of life for these groups ([Frederick et al., 2022](#)), it is important to explore factors related to fatigue, that can be targeted through intervention to reduce fatigue.

However, finding effective treatments is difficult given that the cause of fatigue is often difficult to identify (Ellingson et al., 2014). Behaviour change interventions have been explored as ways to reduce fatigue. More specifically, reducing sedentary time and increasing physical activity (PA) are well-known ways to improve well-being and prevent disease, such as cardiovascular disease and diabetes mellitus (Abrantes et al., 2021; Anderson and Durstine, 2019). Moreover, three comprehensive analyses have indicated that engaging in PA could have positive impacts on decreasing depression (Biddle and Asare, 2011), anxiety (Wipfli et al., 2008), and improving psychosocial wellbeing in adolescents (Spruit et al., 2016). There is now also emerging evidence that sleep and physical activity might independently positively impact energy levels and fatigue among college students (Frederick et al., 2021).

PA is a health-promoting behaviour that shows promise in combating fatigue (O'Connor and Puetz, 2005). Several cross-sectional studies have examined the associations between different intensities of PA as a continuous variable and feelings of fatigue, with mixed results. For example, research has reported a significant relationship between feelings of fatigue and self-reported moderate-to-vigorous PA (MVPA) (Soyeur et al., 2010) as well as device-measured light PA (Tao et al., 2019), but not with device-measured time in MVPA (Tao et al., 2019). The findings are equivocal, with some reporting no associations between PA and fatigue based on self-reports among adolescents (Loureiro et al., 2012). In contrast, others concluded from self-reported data, that adopting health habits such as engaging in PA, was linked to reduced levels of fatigue (Resnick et al., 2006; Yarcheski et al., 2009).

Concerning experimental research among university students specifically, a

low-intensity exercise intervention induced a significant reduction in fatigue (De Vries et al., 2016). Studies in other populations also show that exercise as a form of PA can have positive effects for fatigue in people with burnout syndrome (Gerber et al., 2013), multiple sclerosis (Pilutti et al., 2011), and rheumatoid arthritis (Rongen-van Dartel et al., 2015). Importantly, these improvements have been shown to be comparable to the effects on fatigue of cognitive– behavioural interventions or treatment with medication (Puetz et al., 2008). Interestingly, there is also evidence that withdrawing PA can increase feelings of fatigue (Weinstein et al., 2009).

It is worth noting that sedentary behaviour (SB, any waking behaviour characterised by energy expenditure of  $\leq 1.5$  metabolic equivalents in a sitting, lying or resting position (Tremblay et al., 2017)), has health benefits that are independent of PA and are associated with an increased risk of poor health (Ekelund et al., 2019). Regarding fatigue, associations between sedentary time and fatigue have been examined, with a systematic review reporting that overall sedentary time appears to be positively associated with fatigue in adults (O'donoghue et al., 2016). However, findings from this review were inconsistent, with some studies showing significant associations (where self-reported SB was used) (Kokic et al., 2019), and others reporting no associations (where device-based measures of SB were used) (Tao et al., 2019). Exploring associations between fatigue and SB in university students is interesting, given that students may spend large proportions of the day sedentary during classes and broader study (Moulin and Irwin, 2016; Vella and Nelson, 2023).

It should be noted, that it is possible that there is a bi-directional relationship between PA and SB with fatigue, whereby higher PA and lower SB, could be

both a cause, and a consequence of lower levels of fatigue. Indeed, alongside the research cited above, studies have shown that fatigue can also be predictive of PA and SB ([Hammer et al., 2018](#); [López-Castedo et al., 2018](#); [Metsios et al., 2023](#); [Portela-Pino et al., 2021](#); [Veldhuijzen van Zanten et al., 2015](#); [Viner et al., 2008](#)). However, evidence from experimental studies (e.g. PA interventions) demonstrating changes in PA and SB result in changes in fatigue outcomes post-intervention, suggest there is a role for PA and SB in managing fatigue ([Feldthusen et al., 2016](#); [Katz et al., 2018](#); [Thomsen et al., 2017](#)). As a result, it is important for research to examine in more detail, the associations between both PA and SB with fatigue, considering PA and SB as predictors of fatigue, and addressing limitations of existing research in this domain.

A somewhat global limitation of existing research into the relationship between both PA and SB with fatigue, is that it has almost exclusively explored the associations between these behaviours with fatigue using measures of “general fatigue”, assessed at one point in time. For example, studies typically rely on visual analogue scales (VAS) and numerical rating scales (NRS) asking about an individual’s experience of fatigue generally, over the preceding week or month. However, these questionnaires are simple and unidimensional, and do not consider either the complex, multidimensional nature of fatigue (e.g., distinctions between mental vs. physical fatigue), or the fact that fatigue is dynamic and variable, and can change and fluctuate within or between days.

Ecological momentary Assessments (EMA) offers a methodology to help understand complex dynamic relationships between factors which may fluctuate frequently over time. EMA can help researchers to understand how people feel and act “in the moment”. That is, instead of asking participants to remember

later, participants' emotions and experiences are captured in real time as they go about their daily lives (Shiffman et al., 2008). In the context of understanding fatigue, by measuring fatigue at several points throughout the day and across several days, it is possible to get a more comprehensive view of variations in fatigue over the course of the day. Importantly, it also allows us to explore if behaviours such as PA and sedentary time (ST, a facet of SB that can be measured by devices) are more strongly related to fatigue at different time periods of the day (e.g., in the morning, compared to the afternoon, or the evening (Curran and Bauer, 2011)). This can provide interesting information for the development of interventions. By taking the assessments over the course of a week, it will allow for a more accurate reflection of the overall levels of fatigue experienced during that week. However, to our knowledge, it is currently not known if these daily single-item assessments of fatigue are a stronger predictor of PA and ST than typical assessments of fatigue, which are reflective of an overall week.

To address current research gaps concerning both 1) unidimensional and 2) static (one-point in time) measures of fatigue, the present study utilised an observational and EMA methodology to investigate the relationship between sedentary time and PA and 1) multi-dimensional aspects of fatigue over the previous week, and 2) EMA-based assessments of general fatigue across the day (over a week), among university students. It was hypothesised that; 1) higher levels of PA would be associated with lower levels of all multidimensional facets of fatigue and general fatigue, and 2) higher levels of ST would be associated with higher levels of all multidimensional facets of fatigue and general fatigue.

## **Methods**

### ***Participants and recruitment***

Participants were recruited from the University of Birmingham in the West Midlands (UK) Participants were recruited over a 6-month period, from November 2022 to April 2023. Participants who met the following criteria were eligible: (i)  $\geq 18$  to 30 years of age; (ii) able to speak/read English. Exclusion criterion was a diagnosis of any mental health condition.

### ***Study Design***

This study was a cross-sectional, observational study which utilised questionnaires in conjunction with 7-day objective assessment of physical activity and sedentary behaviour, and ecological momentary assessment (EMA) of fatigue. The study was approved by the University of Birmingham Ethics committee (ERN-19\_1188C), and all participants provided informed consent. The study also respected participants' privacy by providing the option to decline to answer any questions they were uncomfortable with.

### ***Study Procedures***

Interested participants were provided with a participant information sheet. To take part in the study, participants visited the School of Sport, Exercise and Rehabilitation Sciences at the University of Birmingham.

After providing their informed consent, participants completed an online survey which asked participants about demographic factors and their general levels of fatigue. They were then provided with an EMA-enabled accelerometer, the PRO-Diary watch, which was worn on their non-dominant wrist for the

subsequent 7-days. The PRO-Diary watch was used to measure participants self-reported fatigue intensity 3 times a day, as well as their levels of PA and ST. Participants were also asked to complete a paper-based diary throughout the 7-day monitoring period, in which they were asked to report their wake and sleep times of that day. After the 7-day monitoring period, participants returned their PRO-Diary watch and paper diary to the research team where data were downloaded ready for data processing.

## **Measures**

### ***Online survey***

#### ***Demographic information***

This study gathered information from participants on their demographics, including (e.g., age, gender, and ethnicity), as well as whether they engaged in physical activities like sports or exercise.

#### ***Fatigue***

The 20-item Multidimensional Fatigue Inventory (MFI-20;(Smets et al., 1995)) was used to measure different aspects of fatigue including general fatigue (e.g., "I feel tired"), physical fatigue (e.g., "Physically I feel only able to do a little" ), reduced activity (e.g., "I get little done" ), mental fatigue (e.g., "It takes a lot of effort to concentrate on things" ), and reduced motivation (e.g., "I do not feel like doing anything" ). Each subscale comprised of four items and participants rated their level of agreement with each statement on a 5-point Likert scale that ranged from 1 (yes, that is true) to 5 (no, that is not true). The MFI-20 is a reliable and valid tool for measuring fatigue (Smets et al., 1995) and has been

successfully employed in studies involving adolescent populations (Vantieghe [et al., 2018](#)). In this study, the MFI showed high internal reliability (mental:  $\alpha=.79$ : physical:  $\alpha=.75$ : general:  $\alpha=.76$ : reduced motivation:  $\alpha=.77$ : reduced activity:  $\alpha=.77$ ).

### ***Ecological momentary assessment of fatigue intensity (PRO-Diary watch)***

The 7-day monitoring period began on the same day participants completed the survey. During the 7-day period, participants were asked to wear the PRO-Diary watch on their nondominant wrist continuously for 24-hours a day, except while bathing or swimming.

Fatigue intensity: For EMA assessment of fatigue, participants were prompted to self-report their fatigue intensity three times a day. Specifically, three prompts were automatically administered by the PRO-diary watches at randomly selected times between the hours of 11:30 to 12:00 (prompt 1 – reflective of morning fatigue [AM fatigue]), 16:30 to 17:00 (prompt 2 – reflective of afternoon fatigue (PM1 fatigue)), 21:30 to 22:00 (prompt 3 – reflective of evening fatigue [PM2 fatigue]). Each prompt required participants to respond to a question which asked, “How fatigued or tired do you feel right now?” on a scale from 1 (not at all) to 5 (extreme fatigue).

Data collected throughout the week of assessment was downloaded using the PRO-Diary (CamNTEch, Cambridge, United Kingdom) with MotionWare 8 programme (CamNtech). A mean value was calculated for each day segment per participant, providing a measure of mean morning fatigue intensity, afternoon fatigue intensity, and evening fatigue intensity. To be included in the

analyses, the participant had to have at least 4 days of valid fatigue data for morning, afternoon, and evening assessments.

### ***Physical activity and Sedentary time (PRO-Diary watch)***

In addition to the user interface for entering EMA symptom ratings, the PRO-Diary watch has a triaxial micro-electromechanical systems accelerometer, allowing for measurement of PA and ST. The PRO-Diary watch was programmed using the manufacturer proprietary software (MotionWare 8.40, CamNTEch, Cambridge, United Kingdom) to record PA and ST in 60s epochs. intervals. While the system allows for intervals, like 30 second, 15 second 5 second 2 second and 1 second epochs. Previous studies have provided evidence supporting the dependable performance of this accelerometer in assessing both PA and ST. When compared to a widely accepted and thoroughly validated device like ActiGraph™, the accelerometer yielded favourable results in terms of its intra-instrument reliability (Hickey et al., 2016).

### ***Daily Diary***

#### ***Data processing for measurement of physical activity and sedentary time***

Accelerometer data were downloaded and processed using the MotionWare software (version 8.40, CamNTEch, Cambridge, United Kingdom) to generate daily time spent in light, moderate and vigorous PA, as well as ST. All accelerometer data went through extensive data cleaning using a standardized protocol to identify invalid data and to classify sedentary or activity data. Specifically, data from each participant's PRO-Diary watch were downloaded into Microsoft Excel. Accelerometer data was used to identify each epoch based on the intensity of the PA or sedentary using the following cut off points:

vigorous PA ( $\geq 1000$  activity counts per minute), moderate PA ( $\geq 500$  to 999 activity counts per minute), light (50 to 499 activity counts per minute), and ST ( $\leq 50$  activity counts per minute). All data recorded data at the 60-second epoch level were manually checked to identify periods of sleep vs. wakefulness using the acceleration signals, in conjunction with wake/sleep times reported in the daily diary. Next, waking data were examined to identify periods of non-wear. As per the manufacturer's instructions, non-wear periods were identified as -1 values in the data field. Hours with a -1 value within an hour timeframe (e.g., 9:00-09:59, 11:00-11:59) were excluded from analysis as well as hours between midnight and 5am, based on the regular sleep/wake times of the participants. To be included in the analyses, a day had to have at least 10 valid hours (Freedson and John, 2013; Troiano et al., 2008). Subsequently, valid hours were used to calculate a mean value of vigorous PA, moderate PA, light PA, and ST of each day expressed as minutes per hour. Next, the overall mean for each participant using the mean values per day of each valid day. To be included in the analyses, a participant had to have at least 4 valid days of accelerometer data (Aadland and Ylvisåker, 2015; Trost et al., 2005). Finally, the minutes per hour spent on vigorous and moderate PA were combined, to yield a measure of moderate to vigorous PA (MVPA). Therefore, the overall data provided was a value of MVPA, light PA, and ST expressed as mean minutes per hour per participant.

### **Data reduction and Statistical Analyses**

In total, 193 participants were recruited for the study. Due to technical problems (i.e., problems with downloading data 11 participants and lost watch 1

participant), accelerometer data was available for 181 participants. Close inspection of demographic data revealed that some participants had to be excluded because of being too old to participate ( $n=5$ ), and for some participants questionnaire data was not available ( $n=20$ ) or age was missing ( $n=2$ ), resulting in a sample of 154 participants. A further 75 participants were excluded due to not having at least 4 days of valid accelerometer and fatigue outcomes, and 1 participant being excluded because of no available information on age, resulting in a final sample size of 79 participants. Analyses were conducted to explore whether those who were included in the final sample were significantly different from those included in the analyses. Analyses of Variance (MFI fatigue) and Chi-Squared test (gender) revealed no significant differences (all,  $p > .05$ ). There was however a significant difference in age, with those who were included being older (mean (SD) = 21.10 (2.4) years) compared to those excluded (mean (SD) = 19.96 (1.7) years).

Following this, Pearson's correlations were carried out to determine associations between PA and ST variables with all fatigue outcomes, as well as associations between age with PA, ST and fatigue outcomes. In addition, independent samples t-tests examined any gender differences in PA, ST or fatigue outcomes. The results of this analysis were used to determine the need to adjust for age and gender in subsequent regression models.

Main analyses were regression analysis to explore the associations between PA and sedentary time, with different markers of fatigue. We modelled PA and ST as dependent variables, and fatigue outcomes as independent variables. Where significant differences or associations were identified according to age

and gender in preliminary analysis, they were included as covariates in regressions.

## **Results**

### **Participant characteristics**

Participant characteristics are reported in **Table 4.1**. The sample consists of 79 students encompassing slightly more males than females. The age range was from 18 – 30 years, with 82% of participants aged 22 years and under. The majority of participants were of a Caucasian ethnicity (n = 54), with smaller numbers of participants who were Asian Indian (n = 14), Black Caribbean (n = 4), Mixed ethnicity (n = 3), or reporting their ethnicity to be other (n = 2). Two participants did not report their ethnicity. According to measurement of fatigue with the MFI, general fatigue and mental fatigue were reported to be highest across the sample. A repeated measures ANOVA showed a significant time effect for fatigue, over the course of the day ( $F(2, 77) = 22.91, p = <.001, \eta^2 = .373$ ). Post-hoc analysis revealed that fatigue was lowest in the morning, with a significant increase seen in the afternoon (PM 1), and a further significant increase in the evening (PM 2).

**Table 4.1: Participant characteristics**

<b>Demographics</b>	<b>Female (n = 33)</b>		<b>Male (n = 46)</b>		<b>Total (n = 79)</b>	
	<i>Mean ± SD / Range (min-max)</i>		<i>Mean ± SD / Range (min-max)</i>		<i>Mean ± SD / Range (min-max)</i>	
<i>Age (Years)</i>	21.1 ± 2.3	18 - 30	21.1 ± 2.5	18 - 28	21.1 ± 2.4	18 - 30
<i>General fatigue</i>	10.1 ± 2.9*	4 - 16	11.5 ± 2.9	6 - 20	10.9 ± 3.0	4 - 20
<i>Physical fatigue</i>	8.1 ± 3.3	4 - 15	8.5 ± 3.6	4 - 20	8.4 ± 3.5	4 - 20
<i>Mental fatigue</i>	11.3 ± 3.4	7 - 20	11.5 ± 3.8	4 - 20	11.4 ± 3.6	4 - 20
<i>Reduced activity</i>	8.9 ± 3.5	4 - 18	8.6 ± 3.7	4 - 19	8.7 ± 3.6	4 - 19
<i>Reduced motivation</i>	8.6 ± 2.7	4 - 16	8.6 ± 2.7	4 - 16	8.6 ± 2.7	4 - 16
<i>Total fatigue</i>	47.1 ± 10.7	28 - 79	48.7 ± 13.2	24 - 92	48.0 ± 12	24 - 92
<i>AM fatigue</i>	2.2 ± 0.7	1 - 3	2.5 ± 0.7	1 - 3	2.3 ± 0.7	1 - 3
<i>PM 1 fatigue</i>	2.5 ± 0.7	1 - 3	2.7 ± 0.6	1 - 4	2.6 ± 0.7	1 - 4
<i>PM 2 fatigue</i>	2.8 ± 0.7	1 - 4	3.0 ± 0.6	1 - 4	2.9 ± 0.7	1 - 4
<i>Total PA</i>	36.9 ± 6.5	25 - 48	37.9 ± 6.6	17 - 49	37.5 ± 6.5	17 - 49
<i>MVPA</i>	10.9 ± 4.5	5 - 22	10.5 ± 3.6	2 - 18	10.7 ± 4.0	2 - 22
<i>LPA</i>	25.9 ± 4.0	18 - 33	27.4 ± 4.3	14 - 36	26.7 ± 4.2	14 - 36
<i>ST</i>	23.1 ± 6.5	11 - 34	22.1 ± 6.7	9 - 42	22.5 ± 6.6	9 - 42

Note: \*  $p < .05$ , \*\*  $p < .01$  = significantly different from males. **Multidimensional Fatigue Inventory (MFI-20)** = (General, Physical, Mental, Reduced activity, Reduced motivation and Total). **PA** = Physical Activity, **MVPA** = Moderate – Vigorous Physical Activity, **LPA** = Light Physical Activity, **ST** = Sedentary Time. **AM** = Morning, **PM 1** = Afternoon, **PM 2** = Evening, Physical Activity and Sedentary time (minutes per hour).

### **Preliminary analysis**

Results of correlations analysis are reported in **Tables 4.2** and **4.3**. Results revealed no significant associations between any of the PA or ST variables, with fatigue outcomes measured by the MFI (**Table 4.2**), or general fatigue measured by the PRO-diary watch (**Table 4.3**).

T-tests revealed no significant differences in most fatigue outcomes according to gender. However, general fatigue measured by the MFI was significantly higher in males, compared to females (**Table 4.1**,  $t = -2.11$ ,  $p = .04$ ). There were no significant differences in PA and ST outcomes, according to gender (**Table 4.1**).

*Correlation analysis* revealed a significant, negative correlation between MVPA and age ( $r = -0.23$ ,  $p = 0.04$ ), but no significant correlations between age with any other PA and ST variables (total PA ( $r = -0.11$ ,  $p = 0.39$ ), LPA ( $r = 0.05$ ,  $p = 0.65$ ), SB ( $r = 0.11$ ,  $p = 0.33$ )). There were no significant correlations between age with fatigue outcomes, measured via the MFI (general  $r = 0.18$ ,  $p = 0.11$ ), physical  $r = 0.22$ ,  $p = > 0.05$ ), mental  $r = 0.01$ ,  $p = 0.92$ ), reduced activity  $r = 0.15$ ,  $p = 0.19$ ), reduced motivation,  $r = -0.02$ ,  $p = 0.86$  and total  $r = 0.15$ ,  $p = 0.19$ ), or the PRO-diary watch (AM  $r = 0.03$ ,  $p = 0.79$ ), PM1  $r = 0.06$ ,  $p = 0.59$ ), PM2 ( $r = 0.05$ ,  $p = 0.66$ )). As a result, and to ensure consistency across all analyses, age and gender were both included as covariates in all regression analysis.

In **Table 4.2** shows the results of correlations analysis between the PA and ST variables, excluding the effects of age and gender variables with fatigue outcomes measured by the MFI. In **Table 4.3** shows the results of correlations analysis between the PA and ST variables, also excluding age and gender variables with fatigue outcomes measured by PRO-diary watch. Both of results revealed no a significant correlation between Total PA, MVPA, LPA and ST with fatigue outcomes by MFI and PRO-diary watch without age variables.

**Table 4.2:** Correlations between daily levels of PA and sedentary time with multidimensional fatigue outcomes

	Total PA		MVPA		LPA		ST	
	<i>r</i>	<i>p</i> -value						
<i>General fatigue</i>	0.04	0.75	-0.13	0.24	0.18	0.11	-0.04	0.75
<i>Physical fatigue</i>	-0.09	0.42	-0.21	0.06	0.06	0.61	0.09	0.42
<i>Mental fatigue</i>	0.05	0.67	-0.03	0.77	0.11	0.36	-0.05	0.68
<i>Reduced activity</i>	-0.19	0.09	-0.17	0.13	-0.13	0.24	0.19	0.09
<i>Reduced motivation</i>	-0.12	0.28	-0.15	0.19	-0.05	0.65	0.12	0.27
<i>Total fatigue</i>	-0.09	0.43	-0.19	0.09	0.04	0.73	0.09	0.42

Note: All correlations models were without age and gender variables. **Multidimensional Fatigue Inventory (MFI-20)** = (General, Physical, Mental, Reduced activity, Reduced motivation and Total).

**PA** = Physical Activity, **MVPA** = Moderate – Vigorous Physical Activity, **LPA** = Light Physical Activity, **ST** = Sedentary Time. (Physical Activity and Sedentary time (measured in minutes per hours).

**Table 4.3:** Correlations between daily levels of PA and sedentary time with EMA fatigue outcomes

	Total PA		MVPA		LPA		ST	
	<i>r</i>	<i>p</i> -value						
<i>AM fatigue</i>	-0.08	0.47	-0.17	0.14	0.03	0.78	0.08	0.47
<i>PM1 fatigue</i>	0.04	0.73	-0.07	0.56	0.12	0.27	-0.04	0.72
<i>PM2 fatigue</i>	-0.04	0.71	-0.12	0.29	0.05	0.68	0.04	0.72

Note: All correlations models were without age and gender variables. **Ecological Momentary Assessment (EMA fatigue)** = **AM** = Morning, **PM 1** = Afternoon, **PM 2** = Evening.

**PA** = Physical Activity, **MVPA** = Moderate – Vigorous Physical Activity, **LPA** = Light Physical Activity, **ST** = Sedentary Time. (Physical Activity and Sedentary time (measured in minutes per hours).

### **Regression analysis**

**Table 4.4** shows the results of regression analysis between the PA and ST variables, with fatigue outcomes measured by the MFI. Whilst none of the associations were significant, the most consistent associations were observed with the reduced motivation dimension of fatigue, across all types of PA (all negative, and small in effect size), and also with ST (positive, and small in effect

size). Of all the types of PA, MVPA appeared to have the most consistent associations with all fatigue outcomes, demonstrating small, negative associations with all fatigue dimensions, with associations for physical fatigue, reduced activity, reduced motivation and total fatigue, all being between  $\beta = -0.13$  and  $-0.18$ ).

**Table 4.5** shows the results of regression analysis between the physical activity and ST variables, with fatigue outcomes measured by PRO-diary watch. In the morning (AM) and evening (PM2), MVPA demonstrated the strongest associations with fatigue (between  $\beta = -.17$  and  $-.11$ ). Similar sized associations were observed for both total PA ( $\beta = -.11$ ) and ST ( $\beta = .11$ ), in the expected directions.

**Table 4.4:** Associations between daily levels of PA and sedentary time with multidimensional fatigue outcomes

	Total PA		MVPA		LPA		ST	
	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value
<i>General fatigue</i>	0.05	0.69	-0.08	0.46	0.15	0.18	-0.04	0.69
<i>Physical fatigue</i>	-0.05	0.64	-0.16	0.17	0.07	0.57	0.05	0.63
<i>Mental fatigue</i>	0.03	0.79	-0.04	0.74	0.09	0.47	-0.03	0.79
<i>Reduced activity</i>	-0.13	0.27	-0.13	0.26	-0.08	0.50	0.13	0.26
<i>Reduced motivation</i>	-0.17	0.15	-0.18	0.13	-0.09	0.43	0.17	0.15
<i>Total fatigue</i>	-0.07	0.55	-0.16	0.18	0.04	0.75	0.07	0.55

Note: All regression models were adjusted for age and gender. **Multidimensional Fatigue Inventory (MFI-20)** = (General, Physical, Mental, Reduced activity, Reduced motivation and Total).

**PA** = Physical Activity, **MVPA** = Moderate – Vigorous Physical Activity, **LPA** = Light Physical Activity, **ST** = Sedentary Time. (Physical Activity and Sedentary time (measured in minutes per hour).

**Table 4.5:** Associations between daily levels of PA and sedentary time with EMA fatigue outcomes

	Total PA		MVPA		LPA		ST	
	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value	$\beta$	<i>p</i> -value
<i>AM fatigue</i>	-0.11	0.35	-0.17	0.15	-0.01	0.91	0.11	0.35
<i>PM1 fatigue</i>	0.03	0.79	-0.05	0.67	0.10	0.41	-0.03	0.78
<i>PM2 fatigue</i>	-0.07	0.56	-0.11	0.35	-0.00	0.99	0.07	0.57

Note: All regression models were adjusted for age and gender. **Ecological Momentary Assessment (EMA fatigue)** = **AM** = Morning, **PM 1** = Afternoon, **PM 2** = Evening.

**PA** = Physical Activity, **MVPA** = Moderate – Vigorous Physical Activity, **LPA** = Light Physical Activity, **ST** = Sedentary Time. (Physical Activity and Sedentary time (measured in minutes per hour).

## Discussion

This is the first cross-sectional study to investigate the associations between daily physical activity and sedentary time with EMA-based measures of fatigue, alongside multidimensional fatigue outcomes assessed at one point in time.

Results showed no significant associations between PA and sedentary time with either EMA-based fatigue outcomes or multidimensional fatigue outcomes.

However, whilst not significant, regression analysis suggested there may be stronger associations between MVPA and fatigue outcomes compared to light-PA, and particularly for physical fatigue and EMA-based morning (AM) and evening (PM2) fatigue outcomes. In addition, MVPA and sedentary time appeared to have opposite associations of similar strength, for associations with reduced activity and reduced motivation aspects of fatigue.

There are several possible reasons for the lack of significant associations observed. First, whilst an EMA-based measure offers an insight into the dynamic associations between PA and sedentary time with fatigue, the EMA measures used constituted a single item assessment of fatigue. This measure

will therefore not capture the multidimensional aspects of fatigue, which we have advocated are important to explore. To our knowledge, no studies have used a multidimensional measure of fatigue in an EMA setting. This is perhaps not surprising given that EMA assessments typically involve brief measures to reduce the participant burden. It should therefore be acknowledged that it is possible that the EMA based measure of fatigue did not capture fatigue per se. Participants were asked, “how fatigued or tired do you feel right now?”, where fatigue and tiredness may be perceived differently among this population. Indeed, when exploring the different perceptions of fatigue and tiredness, it was found that students reported variations in meanings of tiredness and fatigue (Long et al., 2022). Therefore, the importance of having definitions and considering the context of fatigue has been emphasised when trying to explore fatigue in more detail (Abbiss and Laursen, 2007).

Concerning results of both multidimensional fatigue and EMA-based fatigue outcomes, it is also important to consider that fatigue can be influenced by several factors, including lifestyle choices beyond PA (e.g. nutrition) and cognitive abilities (Lee et al., 2007; Yang and Cho, 2013). For example, research suggests that slower motor processing and reduced working memory and attention are linked to increased fatigue (Mizuno et al., 2011). Emotional intelligence is also connected to levels of fatigue, and factors such as depression, anxiety, and the quality of sleep influence this relationship (Brown and Schutte, 2006). Future research should explore other factors that may influence the relationship between PA and fatigue, to ascertain the presence of combined, interdependent, or mediated associations. For example, whilst associations between MVPA and sedentary time with fatigue outcomes were

not significant, these associations were opposite in direction and similar in magnitude for reduced activity and reduced motivation dimensions of fatigue – this may indicate these behaviours may operate interdependently when considering associations with these fatigue outcomes in particular.

Existing studies exploring associations between PA, sedentary time and fatigue in populations of young adults and college students, have reported similar/contradictory findings to those observed in this study. For example, when examining simple correlations, some studies indicate no correlation between physical activity and fatigue ([Loureiro et al., 2012](#)). On other hand, some studies indicate no associations between ST and fatigue ([Frederick et al., 2022](#)), whereas others reported PA was associated with fatigue ([Gillham, 2023](#); [Hanif et al., 2024](#)). For example, engaging in total PA was negatively associated with fatigue, vigorous PA was negatively associated with all fatigue outcomes except for mental fatigue, moderate PA was negatively associated with all fatigue outcomes, whereas walking was only negatively associated with reduced activity ([Gillham, 2023](#)). Another study found higher levels of PA were related to lower levels of fatigue among university students ([Hanif et al., 2024](#)). There are two possible reasons for the lack of significant associations in our study compared to the above studies. First, the differences in the way PA was calculated, e.g. cut points. In previous studies, self-reporting for weekly MET minutes were determined by multiplying the time spent on activities by their MET values ([Gillham, 2023](#); [Hanif et al., 2024](#)), whereas our study utilised accelerometer readings to classify physical activity intensity based on PA counts per minute following the manufacturers guidelines. Second, there were differences in mean values of fatigue in our sample compared to previous work,

which could have impacted the findings. For example, the levels of fatigue in our study were higher compared to the previous study in students (Gillham, 2023), whereas mental fatigue, reduced activity and reduced motivation were slightly lower. Another study used a different way to measure fatigue, which makes this comparison difficult (Hanif et al., 2024).

The sample size of the current study was limited, which may have reduced the statistical power of the analysis undertaken. Indeed, whilst no associations were significant, there were stronger associations for MVPA compared to light PA for some fatigue outcomes (e.g., physical fatigue and EMA-based morning (AM) and evening (PM2) fatigue outcomes). This may offer a preliminary indication that higher intensities of PA may be more relevant when considering the relationship between PA and fatigue among university students. In line with this suggestion, a previous EMA-based study reported some associations between MVPA and subsequent levels of fatigue (Liao et al., 2017b).

Based on our analysis, we found that there were no associations between most multidimensional aspects of fatigue, and EMA-related measures of fatigue with age in this study. A previous study found an association between age and fatigue (men mentioned experiencing fatigue compared to women while younger students showed levels of fatigue) (Amaducci et al., 2010). In an EMA-based study of participants with Multiple Sclerosis, no associations between age and fatigue reported 5 times a day were reported (Kratz et al., 2019). The causes of possible variations in findings regarding associations between age and fatigue are not fully understood. Certain research studies have proposed that it could be linked to aspects like the quality of sleep and levels of physical

activity (Christie et al., 2016). More investigation is necessary to delve into the possible factors that could explain the associations between age and fatigue.

The strengths of this study are the innovative EMA-based study design to examine associations between PA and sedentary time with fatigue reported throughout the day. In addition, these associations were examined alongside a more global, but multidimensional measure of fatigue – the MFI, enabling an evaluation of the PA/sedentary time and fatigue relationship, from different perspectives. However, limitations of the study include a small sample size, which may have limited the ability to detect significant relationships. In addition, the sample was limited to students from one university, most studying the same degree. Different results may have been found where a more diverse population was recruited, and thus, findings are not generalisable beyond the current population.

## **Conclusion**

The current study suggests there are no associations between daily PA and sedentary time in relation to multidimensional aspects of fatigue in university students. In addition, where momentary based measures of fatigue were employed, associations were still not evident. Further research in larger, more diverse samples, using validated momentary measures of fatigue are required, to explore these associations in more detail. In addition, studies should consider measuring other factors that may influence the PA/sedentary time and fatigue relationship (e.g. sleep, stress).

## **CHAPTER 5**

### **CHAPTER 5: GENERAL DISCUSSION**

The research included in this thesis contributes to our understanding of the role of physical activity, exercise, and sedentary behaviours for fatigue, with a specific focus on individuals with Rheumatoid Arthritis (RA). In addition, this thesis pilots the application of a novel EMA-based method to examine dynamic associations between physical activity and sedentary time with fatigue, that could be usefully applied to the RA population in Chapter 4. The sections below outline the findings of this research, suggests possible future research directions and practical applications of the research and identifies limitations of the studies comprising this thesis.

**Key findings of the research conducted within this thesis:**

- 1. Overall, observational and intervention studies in RA suggest that there is a positive association and/or impact of PA and exercise behaviours on fatigue in this patient group.***

The precise factors and indicators of fatigue in RA, such as the impact of exercise remain incompletely understood ([Druce and Basu, 2019](#); [Nikolaus et al., 2013](#)). Indeed, the association between exercise and fatigue in individuals with RA is intricate and varied. Results from the review conducted in Chapter 2 suggest that overall, there is a role for both PA and exercise for fatigue in RA. Interestingly, evidence from observational research is stronger for PA, whereas evidence from interventions lends its support more specifically to exercise. The differences in study results observed between PA and exercise may stem from how these activities are measured in the studies. For example, when measuring exercise,

participants are frequently asked to indicate their levels of exercise engagement in reference to categories (e.g., yes/no to meeting physical activity guidelines, or engagement in <30 mins/day vs. 1 hour/day vs. >2 hours/day). In contrast, PA is often assessed using measures that enable PA levels to be quantified in a more linear and continuous manner (e.g., total minutes/day). Therefore, the most common approach used to measure PA, either device-based or subjectively, allows greater variability in physical activity levels to be captured, meaning associations with fatigue are more likely to be identified.

***2. Existing exercise and PA interventions vary considerable in terms of their design and content. However, the cumulative evidence suggests that supervision may be particularly important to consider in the design of exercise interventions, and behavioural support is likely to be a key component contributing to effectiveness across both exercise and PA interventions.***

In **Chapter 2**, roughly half of the exercise interventions showed increases in exercise levels leading to reduced fatigue for people living with RA. However, the interventions were highly heterogenous in terms of their design and content (e.g., type of exercise, intervention duration, supervision or support provided). This diversity makes it challenging to interpret the results. Despite these challenges, synthesis of the research in this area provided the opportunity to understand factors that are important to consider in the design of exercise interventions. Firstly, one strength of this review is that it encompassed exercise interventions targeting a variety of exercise types such as aerobic exercise, resistance training, and yoga. Most of the interventions focused on aerobic

exercise training with fewer focusing on resistance or other structured exercises. Considering that the type of exercise may impact intervention effectiveness and outcomes related to RA (e.g., aerobic exercise may have a greater benefit overall health while strength training may be more effective at improve function), it is important to consider the type of exercise when designing interventions based on goals and outcomes in line with the aims of the work. Furthermore, more research exploring types of exercises should be conducted to better understand their specific benefits, and particularly their benefits for fatigue, which could guide intervention design and recommendations. Secondly, exercise interventions that included a supervised component, and both PA and exercise interventions that included an element of behavioural support, seemed to more consistently report significant reductions in fatigue. Overall, findings from the review align with research, in showing that fatigue is an individualised phenomenon, suggesting that a variety of behavioural approaches might be necessary to address it effectively (Neill et al., 2006). Therefore, it is important to understand the associations between fatigue and PA or exercise in more detail to be able to design interventions that specifically target fatigue. **Chapter 3** includes the assessment of the diurnal variations in PA and its association to different dimensions of fatigue to explore if interventions should focus on a specific time of day to have the greatest impact on fatigue.

### ***3. There are a lack of studies focusing on the relationship between sedentary behaviour and fatigue in RA.***

Most of the studies in the review conducted in **Chapter 2** explored the role of PA or exercise for fatigue in RA. Relatively few observational studies examined

associations between sedentary behaviour and fatigue, and there were few interventions targeting sedentary behaviour. Studies focussed on sedentary behaviour have shown some preliminary evidence that this behaviour may be associated with fatigue in RA, but more research specifically exploring sedentary behaviours is required to understand whether reducing sedentary behaviour offers a possible avenue for fatigue interventions.

**4. Measurement of fatigue is highly heterogenous and more consistency in measurement tools is required to better understand fatigue in RA.**

**Chapter 2** highlighted that the body of research examining the role of physical activity, exercise, and sedentary behaviour for fatigue in RA patients is characterised by methodological weaknesses in the measurement of these outcomes. Specifically, RA -related fatigue was measured using 16 different instruments in observational studies and 13 different instruments in intervention studies. In 2007, Hewlett and colleagues conducted a review of fatigue measures in RA and reported that 23 scales were used in research ([Hewlett et al., 2007](#)). They reported that only 6 of these scales (including both unidimensional and multidimensional assessment tools) demonstrated adequate validity for measurements of fatigue in RA. The absence of uniformity in fatigue assessment poses a challenge in RA research, making it difficult to compare findings across studies, or setting standards for evaluating fatigue in RA. Theoretically, different domains of RA-related fatigue could be improved by different types of interventions. For example, it is plausible that exercise may primarily improve the physical or general dimension of RA-related fatigue, while other dimensions, such as mental fatigue, may be more responsive to

behavioural interventions, such as those targeting SB. In **Chapter 3**, diurnal patterns of PA and SB were explored among individuals with RA. We also explored how these patterns relate to different facets of fatigue measured by the Multidimensional Fatigue Inventory (MFI-20).

***5. People living with RA tend to be more sedentary and less active (less standing and stepping) in the evening, compared to the morning or afternoon.***

**In Chapter 3**, we addressed two gaps in the research identified in **Chapter 2**. First, we explored associations between device-measured sedentary time and fatigue in RA (alongside standing and PA), using the gold standard measure of sedentary time (the activPAL™) (Chastin et al., 2018). Second, we employed a multidimensional measure of fatigue, that has been validated for use in this population (Goodchild et al., 2008). Specifically, this study examined how different behaviours measured by the activPAL™ device (sitting, standing, stepping and step intensity) relate to patterns of MFI measured fatigue throughout the day for individuals with RA. The findings suggest that during the evening, individuals with RA tend to sit more, stand less, and take fewer steps, compared to earlier parts of the day. Moreover, step intensity is lower in the evening than in time periods (morning/afternoon). A recent study used a similar methodological approach but used an accelerometer (GT3X device) to assess physical activity and sedentary time (LPA, MVPA and SB) as minutes per hour to analyse variations in time and different intensities of physical activity during morning, afternoon, and evening among individuals with RA. The previous study revealed trends to those identified here; sedentary time and lower light and

moderate, to vigorous intensity physical activity in the evening compared to earlier times of the day ([Fenton et al., 2020](#)).

**6. *Sedentary time, standing and stepping are differentially associated with dimensions of fatigue in RA, with stepping behaviours (time and intensity) demonstrating the most consistent associations across all fatigue dimensions.***

The methodology employed in **Chapter 3** also allowed for an exploration of how different movement patterns throughout the day may be linked to the multidimensional aspects of fatigue in people living with RA. Results indicated that stepping time and step intensity were more consistently associated with multidimensional fatigue outcomes across the day. Specifically, the amount of time spent stepping and the intensity of each step was associated with general fatigue, physical fatigue, reduced activity, and reduced motivation. Mental fatigue was the only dimension of fatigue demonstrating no association with stepping time or intensity. This finding is in contrast to previous research goes against research, which reported a correlation between light physical activity and mental fatigue in people with RA ([Brady et al., 2021](#)), and could perhaps be due to differences in measures used to assess PA (i.e. self-report in Brady et al. vs. the activPAL device in this thesis).

Concerning sedentary time, our results showed sedentary time was only significantly positively associated with reduced activity and reduced motivation. This contrasts with previous research, which has shown positive associations between sedentary time with all MFI fatigue dimensions ([Thomsen et al., 2017](#)). In addition, two studies have reported significantly positive associations

between overall self-reported daily sedentary time and physical fatigue in RA (Brady et al., 2021; Løppenthin et al., 2013). As before, it is likely that the differences in these associations are due to the methods used to assess sedentary behaviour (i.e., objective assessment in the current work vs self/report in previous studies).

Overall, the results from **Chapter 3** suggest that interventions that aim to support stepping behaviours may offer a valuable approach toward fatigue management in RA. Therefore, both diurnal patterns of behaviour and associations with fatigue should be considered in intervention design. Prior to intervention, longitudinal research enabling investigation of the dynamic associations between movement behaviours and multidimensional aspects of fatigue in RA are required. Indeed, fatigue is a complex and dynamic experience, and most research studies exploring how PA and SB are linked to fatigue in RA have relied on asking people to remember their feelings of fatigue retrospectively, over a static timeframe (e.g., the previous week or month). When we think about how PA and SB influence feelings of fatigue in RA it is likely that changes in these behaviours will cause fatigue levels to go up and down, which cannot be accurately captured by asking about someone's experience of fatigue over a long period of time. Employing methods such as Ecological Momentary Assessment (EMA) could offer an insight into the evolving connections between movement behaviours and fatigue in RA as demonstrated in **Chapter 4**.

**7. Ecological Momentary Assessment can be used to assess momentary fatigue in research studies examining the role of PA and**

***sedentary time, but the design EMA-based questions should capture the multidimensional aspects of fatigue.***

In **Chapter 4** of this thesis, an EMA-based measure of fatigue was employed alongside a device-based measure of PA and sedentary time, to explore whether daily PA and sedentary time were associated differentially with fatigue measured at different time periods across the day. University students were the population used in this study as a convenience sample, to pilot the EMA methodology prior to its possible application in RA. Results revealed no significant associations between PA and sedentary time with fatigue. This is likely due to the fatigue that the measure of fatigue was too simplistic (i.e. a single item measure), combined with possible differences in how the question was perceived by the population. As such, concerning the intention of this chapter to pilot the EMA methodology, the results showed the methodology could be delivered as intended, but that the measures of fatigue would need to be re-developed before use in RA. Specifically, the results of this chapter underline the importance of defining what is meant by fatigue for the population of interest (in this case, people living with RA), ahead of designing EMA-based questions to try and capture the multidimensional and complex nature of fatigue according to the target population.

***8. Daily PA and sedentary time were not associated with multidimensional aspects of fatigue in university students.***

In addition to exploring associations between PA and sedentary time with an EMA-based measure of fatigue in university students, **Chapter 4** aimed to

compare EMA-based fatigue outcome to multidimensional fatigue outcomes, assessed at one point in time (i.e., a more static, but multidimensional measure of fatigue). Compared to our results in **Chapter 3** (in a population of people with RA), results reported no significant associations between daily measures of PA and sedentary time with multidimensional fatigue outcomes in our sample of university students. This null finding may be due to the small sample size in this study, or perhaps differences in the measurement or complexities of fatigue in the population of interest. For example, for university students, it is possible other factors (e.g., sleep, cognitive function) may influence the association between PA and sedentary time with fatigue outcomes, to a greater extent than is perhaps the case for people living with RA. In addition, results may differ due to the prevalence of physical activity, sedentary time and fatigue in the population of university students, compared to people living with RA (and other studies of young adults that have shown significant associations). Typically, fatigue is higher, levels of PA lower, and sedentary time higher among clinical groups (e.g. people living with RA), compared to young adults (O'Brien et al., 2021; Paul et al., 2014). It is also important to compare the levels of fatigue in the current sample with previous work. As mentioned earlier, there are some variations which could impact on the reported associations. Future research should look at recruiting healthy participants with a broader range of fatigue to explore this in more detail. This higher prevalence (and increased variability) of ST and fatigue, and lower levels of PA in people living with RA, may explain why significant associations were observed in Chapter 3, compared to Chapter 4. Indeed, not only did we report significant

associations between PA and sedentary time with fatigue outcomes in Chapter 3, but other studies in RA have reported positive and negative associations between physical activity and sedentary time with all MFI fatigue dimensions (Brady et al., 2021; Løppenthin et al., 2013; Løppenthin et al., 2015). For example, one study reported significant negative associations between predicted regular PA and physical fatigue (Løppenthin et al., 2015), with another demonstrating significant negative associations between light physical activity and mental fatigue (Brady et al., 2021). In regards to sedentary time, studies in RA have also reported significant positive associations between overall self-reported daily sedentary time and physical fatigue in RA (Brady et al., 2021; Løppenthin et al., 2013).

Nevertheless, whilst we did not observe significant associations between PA and sedentary time with fatigue in our sample of University students, other studies have reported contrasting findings, whereby PA of different intensities showed associations with different aspects of fatigue (Gillham, 2023).

Focussing on ST, self-reported ST was reported to be related to feelings of fatigue (Kokic et al., 2019). However, it is worth to note that no studies have explored the relationships between ST and fatigue using a comprehensive measure such as the MFI-20. Additional research seeking to explore the role of both PA and sedentary time with multidimensional fatigue outcomes is therefore required, to understand these complex and dynamic relationships across highly variable population demographics. This is critical prior to developing interventions which seek to improve fatigue in the target population. Indeed, understanding which dimensions of fatigue (if any) are more likely to be

responsive to changes in PA and sedentary time within a particular population is key to intervention efficacy.

## **Practical Implications**

The practical implications can be summarised as followed:

Firstly, non-Pharmacological interventions should be integrated into RA care, to help manage fatigue: This combined approach aims to help alleviate symptoms manage disease activity and improve wellbeing. Results from this thesis are in line with research that suggests non-pharmacological interventions centred on increasing PA and exercise may be beneficial in mitigating effects as fatigue in individuals with RA ([Santos, Duarte, Marques, et al., 2019](#)). Furthermore, the recent EULAR recommendations for the management of fatigue in inflammatory rheumatological and musculoskeletal diseases state that patients should be provided with physical activity advice to manage their fatigue ([Dures et al., 2023](#)). However, additional research which considers the complexities and dynamic nature of the experience of fatigue in RA is required, alongside more consistency in measurement approaches (of both PA/exercise and fatigue), to better understand the associations between PA and exercise with fatigue in RA, prior to intervention.

Secondly, supervision and behavioural support may improve the intervention adherence and subsequently, effectiveness: results from **Chapter 2** demonstrate supervision of exercise is proven to lead to enhancements in exercise levels and reductions in fatigue. Moreover, integrating behavioural support components into interventions seem to increase the likelihood of maintaining engagement in activities and exercises. It is recommended to utilise

evidence-based behaviours change strategies and ensure that interventions are rooted in theories.

Third, interventions that focus on stepping may offer promise for reducing fatigue in RA: based on the findings discussed in **Chapter 3**, it could be recommended that stepping behaviours (time and intensity) could offer a feasible intervention target for fatigue management in RA, given this behaviour was most consistently associated with multidimensional fatigue outcomes.

Previous PA interventions focussed on walking in RA have shown some promise for reducing fatigue in RA (Katz et al., 2018). A consideration of the timing of steps/walking (e.g. morning vs. evening), alongside the step intensity, may offer potential to further enhance effectiveness of such interventions.

Finally, aiding understanding of the complexities in defining and measuring PA, sedentary time and fatigue in different populations: The combined insights, from (**Chapters 3 and 4**) of this thesis shed light on the relationships between PA, sedentary time and fatigue in different groups, but also the complexities of assessing movement behaviours and multidimensional and dynamic aspects of fatigue in different populations. Specifically, these findings underscore the importance of considering how fatigue is defined, and subsequently measured in different populations, prior to seeking to understand associations.

## **Limitations**

The objectives of this thesis were to evaluate the associations between exercise, physical activity, and sedentary behaviour with fatigue among people living with RA, using methods which move beyond simplistic single item measures – specifically using EMA and multidimensional measures of fatigue.

Acknowledging the limitations of the research is important when interpreting the results, in addition to recognising its strengths. Overall, the number of participants in **Chapters 3** and 4 were quite limited. The small sample size may have influenced the chances of uncovering significant associations. The generalisability of results also needs to be considered – in **Chapter 4**, 60% of the participants were male and the majority of the participants were undergraduate students from a sport and exercise science degree programme. As such, results from **Chapter 4** are not generalisable beyond a student population. Considering study design, both **Chapters 3** and **4** were cross sectional studies. This method provides a view of associations at a single point in time but falls short in capturing the changing or enduring links between PA and sedentary with fatigue.

### **Future research directions**

The limitations of the research undertaken in this thesis, point to the need for future research in larger, and more diverse populations. For example, studies of RA should be larger, and include participants of varying age, sex, and disease severity levels, to better understand the associations between PA, sedentary time and fatigue in this population. Studies in university students or young adults should ensure diversity across key demographics, and consider including diverse populations that demonstrate variability in other factors which may influence associations between PA, sedentary time and fatigue (e.g., degree programme, level of educational attainment). In addition whilst Chapter 4 did provide some insight into the dynamic associations between PA and sedentary time with fatigue in a population of university students, future studies adopting a

longitudinal approach and employing methods such as EMA should be conducted, to provide a more comprehensive understanding of the dynamic associations between PA and sedentary time movement patterns with fatigue in RA, and other populations.

## **Conclusion**

The combined findings of this thesis indicate a plausible role of increasing PA (including exercise) for managing fatigue in RA (seen in **Chapters 2 and 3**). However, limited evidence exists for the role of sedentary time (**Chapters 2, 3, and 4**). In all cases, more research is required to uncover the complexities of the associations between these movement behaviours and fatigue in RA, particularly when considering the complex and multidimensional nature of the experience of fatigue (**Chapters 3 and 4**). EMA-methods employing multidimensional measures of fatigue, alongside device-based assessments of PA and sedentary time, may show some promise, but further development and validation work of fatigue measurement is required prior to implementing such studies in RA (**Chapter 4**). Based on the current evidence it seems reasonable to suggest that where interventions are deemed valuable, supervised, and behavioural support components may be more effective than interventions without these components (**Chapter 2**). In addition, diurnal patterns of PA and sedentary time are important to consider when thinking about optimal windows to encourage changes in movement behaviours (**Chapter 3**).

## Appendix 2.1: PICO method for search strategy

<b>PICO</b>	Key Words
<b>Population</b>	Humans(s) NOT animals, Adult, Rheumatoid arthritis, Rheumatoid, Rheum, Rheumatology, Arthritis, Arthriti, Disease, Condition.
<b>Intervention</b>	<p>Exercise, exercise programmes, dynamic exercise programs, muscle training, aerobic training, strength training, resistance training, aerobic cardiorespiratory training, muscle strength, muscle strengthening, aerobic, endurance, high intensity versus, sport, gym, walking, running, cycling, jogging, swimming, hydrotherapy, water therapy, pool therapy, exercise therapy, rehabilitation, Pilate, yoga, Tai Chi, (Tai Chi), (taichi).</p> <p>Physical activity, physical fitness, motor activity, physical function, physical training, physical exertion, activities of daily living, physical therapy modalities, low-intensity physical activity, lifestyle/life-style physical activity.</p> <p>Sedentary Behaviour (UK), sedentary Behavior (US), lifestyle/life-style behaviour, sedentary, sitting, sitting time, sitting behaviour, screen time, sedentary lifestyle.</p>
<b>Comparison</b>	<p>The associations between physical activity, exercise, and SB with fatigue.</p> <p>Exercise or lifestyle PA, lifestyle PA or SB.</p> <p>Advice PA or SB.</p> <p>Advice Exercise or lifestyle PA.</p> <p>Placebo intervention.</p> <p>Usual care.</p>
<b>Outcomes</b>	Fatigue, tiredness, weary, weariness, exhaustion, exhausted, apathy, lassitude, weak, lethargy, weakness, asthenia syndrome, asthenic syndrome.

Intervention(s)  
 Randomised (UK)  
 Randomized (US)  
 Randomised Controlled Trial (UK)  
 Randomized Controlled Trial (US)  
 Simple Random Samples  
 Controlled Clinical Trial  
 Randomly  
 Random  
 Random Allocation  
 Placebo  
 Single-Blind Method  
 Double-Blind Method  
 Trial  
 Groups

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