

**ADVANCES IN PHYSICAL ACTIVITY
PRESCRIPTION IN RHEUMATOID ARTHRITIS
AND THE INFLUENCE ON CARDIOVASCULAR
RISK**

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Abstract

There is a plethora of evidence that people living with rheumatoid arthritis (RA) demonstrate reduced engagement in physical activity (PA) and exercise in comparison to their non-RA counterparts (Lee et al., 2012b, Summers et al., 2019). This has been demonstrated in multiple ways, such as device-based accelerometry measurements (Pioreschi et al., 2013) and self-reported questionnaires (Sokka et al., 2008). Physical inactivity is a known traditional cardiovascular disease (CVD) risk factor, that has been observed to increase CVD risk in people living with RA (Metsios et al., 2009). Indeed, CVD represents the primary cause of mortality in people living with RA (Kitas and Gabriel, 2011). The ~50% increased CVD risk in people living with RA compared to the general population (Agca et al., 2017) is explained by both traditional (e.g., physical inactivity, hypertension) and specific novel RA (e.g. systemic inflammation) risk factors (Skeoch and Bruce, 2015). It has been suggested that these risk factors should be considered collectively to have the best possible impact on reducing CVD risk (Liao and Solomon, 2013, Skeoch and Bruce, 2015).

PA represents a modifiable CVD risk factor in RA that may benefit both disease symptoms as well as CVD risk. As such, it is important to assess the latest novel advances in PA prescription for people living with RA, due to their known inactivity, in order to positively impact these patients holistically in terms of their disease specific issues and overall health. It is equally important to examine vascular function in people living with RA as changes in vascular structure and function across the vascular tree may be involved in the development of CVD and are also modifiable. Previous research has observed mixed findings in various vascular, though the cerebrovasculature in particular is an under researched area in the RA population, despite emerging evidence of links between RA and cerebrovascular disease (Wiseman et al., 2016).

The overarching aim of the body of work described in this thesis was to explore advances in PA prescription for people living with RA, as well as assessing the influence this may have on CVD risk. In addition, previous literature employing exercise interventions in people living with RA was examined in order to assess its quality and try to understand potential reasons why people with RA remain inactive despite the known benefits.

Chapter 3 examined the feasibility and acceptability of a home-based exercise and PA intervention supported by mHealth technology, and a home-based exercise intervention supported by the provision of virtual exercise resources in sedentary individuals, as well as remote data collection techniques. Anthropometric and PA data were collected remotely prior to and following a home-based exercise intervention incorporating i) mobile health (mHealth) technology and exercise counselling, or ii) online resources only. Semi-structured interviews to explore participant experiences were conducted pre- and post-intervention. Data provided novel evidence that both interventions had a positive impact on exercise behaviour, though preliminary outcome data demonstrated greater improvements in PA and adherence to exercise prescription were evident in the mHealth technology supported intervention. This included a greater increase in moderate-to-vigorous PA (MVPA) completed in 10-minute bouts (MVPA+10) in the mHealth group (58 min/wk; CI= -0.06, 0.98, d= 0.47) compared to the online resources group (14 min/wk, CI= -0.32, 0.54, d= 0.12). Moreover, data also revealed that remote data collection techniques were a feasible approach to obtain data. Positive participant perceptions of both the mHealth supported exercise intervention and remote data collection techniques reinforced the feasibility of both remote interventions and data collection.

Chapter 4 utilised both the mHealth supported intervention style and remote data collection piloted in *Chapter 3* by examining the effectiveness of an mHealth technology supported intervention to increase PA levels in people living with RA. Secondary to this, the

study assessed adherence and compliance to the intervention, and the effect on basic clinical outcomes, quality of life and disease activity. Fifty people with RA were randomised to either MOTIVATE RA (mHealth supported walking intervention) or conventional care (CC) groups. Both groups underwent the remote assessment of general health and disease outcomes, anthropometrics and PA prior (T1) to and after (T2) a 12-week intervention period, followed by a three-month optional follow-up assessment (T3). The MOTIVATE RA group demonstrated greater levels of PA at the end of the intervention compared to the CC group, though it is important to note that no outcomes reached statistical significance. The MOTIVATE RA group were performing 103 minutes (95% CI = -17, 224; $P = 0.09$) more MVPA than the CC group at T2. Additionally, the MOTIVATE RA group's average accelerations were observed to be 1.2mg/day (95% CI = -3.5, 5.8; $P = 0.61$) higher than the CC group, crossing the threshold for a minimal clinically important different (MCID). Though there were limited differences in health and disease symptom related outcomes between groups ($P > 0.05$). Adherence (73%) and compliance (91%) within the MOTIVATE RA group provided evidence that the intervention was feasible for people living with RA. Exploratory analysis of optional three-month follow up data in a subset of participants revealed no significant group*time interactions ($P > 0.05$). The study demonstrated that mHealth technology supported interventions are feasible for people living with RA and data indicated that such interventions may elicit clinically meaningful change, via increases in MVPA.

Chapter 5 explored the impact of RA on micro-, macro- and cerebrovascular function in comparison to matched controls via the concurrent assessment of vascular function across the vasculature tree. Seven females with a clinical diagnosis of RA and 8 female non-RA control participants were recruited to undergo a battery of vascular assessments including; endothelial function via brachial and femoral artery flow-mediated dilation assessment,

cutaneous microvascular function assessment via response to post-occlusive reactive hyperaemia (PORH) and cerebrovascular function via measurements of cerebral reactivity to CO₂ and cerebral autoregulation (CA). These preliminary data demonstrated microvascular dysfunction in people living with RA in both the upper and lower limbs. Peak cutaneous vascular conductance (CVC) in the RA group was lower than in the control group, though this did not reach statistical significance ($-0.37 \text{ PU.mmHg}^{-1}$, 95% CI = $-0.82, 0.08$, $P = 0.10$). The %base-peak in the RA group was lower than in the control group, though this did not reach statistical significance (-94% , 95% CI = $-202, 15$, $P = 0.08$). Vascular dysfunction was also present in people living with RA in the macrovasculature, though only in the lower limbs, with upper limb flow-mediated dilation (FMD) similar between RA and control groups. There was no difference in allometrically scaled FMD% in the RA group compared to their non-RA counterparts (-0.2% , 95% CI = $-1.9, 1.5$, $P = 0.78$). Allometrically scaled FMD% was lower in the RA group than the control group but was non-significant (-1.5% , 95% CI = $-3.2, 0.3$, $P = 0.09$). Finally, it was identified that there was no difference between the RA group and control group for cerebral reactivity to CO₂. Absolute and relative gain of cardiovascular reactivity to CO₂ (CVR_{CO2}) and CVR_{CO2MAP} (accounting for the effects of mean arterial pressure [MAP] changes on CVR_{CO2}) during CO₂ inhalation was not different between the RA and control groups ($P > 0.05$, Table 5). Interestingly, dynamic cerebral autoregulation (dCA) appeared to demonstrate a more efficient response in the RA group compared with the control group. Normalised gain was lower in the RA group than in their non-RA counterparts, though this did not reach statistical significance ($-0.29 \text{ \%cm.s}^{-1}.\text{mmHg}^{-1}$, 95% CI = $-0.58, 0.00$, $P = 0.05$). Though these preliminary data constituted a low sample size and lack of statistical power, as well as the absence of normative values making it hard to draw firm conclusions from these data. Overall, it was demonstrated that people living with RA may exhibit vascular dysfunction in both the micro- and macrovasculature, whilst the cerebrovascular appears unaltered.

Chapter 6 employed a systematic scoping review to summarise existing exercise interventions utilised in randomised controlled trials (RCTs) involving individuals living with RA. This review assessed their level of reporting applying the Consensus on Exercise Reporting Template (CERT). Interventions involved a combination of supervised aerobic and resistance exercise completed over ~3 sessions per week, lasting a total of ~147-162 minutes, most often at a moderate intensity. Exercise intervention reporting quality was poor, the median score was seven (range 1-13) out of 19. Thirteen exercise interventions had a CERT score of ≥ 10 , while the remaining 37 interventions (74%) all scored < 10 . This review demonstrates that the quality of reporting for exercise interventions designed for people living with RA is very poor. Significant improvements to reporting are needed in order to enable quality replication and improve translation into clinical settings.

Collectively, the data contained within this thesis suggests that remote mHealth technology supported interventions are feasible for people living with RA and may elicit clinically meaningful changes in PA behaviour, with remote data collection techniques being feasible and successful in monitoring such interventions. Increasing PA is an important management strategy for RA as this thesis has also shown people living with RA may have vascular dysfunction across the vascular tree, which leads to increased CVD risk. Moreover, future research employing exercise interventions in people living with RA, in attempts to upregulate PA and lower CVD risk, need to significantly improve reporting standards in order for findings to translate to a clinical setting.

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Declaration

I declare that the work within this thesis is entirely my own.

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Other publications completed by the candidate during PhD tenure

Bannell, D.J.*, Montrezol, F.T.* , Maxwell, J.D., Somani, Y.B., Low, D.A., Thijssen, D.H. and Jones, H., 2023. Impact of handgrip exercise and ischemic preconditioning on local and remote protection against endothelial reperfusion injury in young men. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 324(3), pp.R329-R335.

Maxwell, J.D., **Bannell, D.J.**, Brislane, A., Carter, S.E., Miller, G.D., Roberts, K.A., Hopkins, N.D., Low, D.A., Carter, H.H., Thompson, A. and Claassen, J.A., 2022. The impact of age, sex, cardio-respiratory fitness, and cardiovascular disease risk on dynamic cerebral autoregulation and baroreflex sensitivity. European Journal of Applied Physiology, 122(6), pp.1531-1541.

Peçanha, T., **Bannell, D.J.**, Sieczkowska, S.M., Goodson, N., Roschel, H., Sprung, V.S. and Low, D.A., 2021. Effects of physical activity on vascular function in autoimmune rheumatic diseases: A systematic review and meta-analysis. Rheumatology, 60(7), pp.3107-3120.

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List of abbreviations

Abbreviation	Title
ACA	Anterior cerebral artery
ACPAs	Anti-citrullinated protein autoantibodies
ACR	American College of Rheumatology
AE	Aerobic exercise
AEv	Adverse events
AUC	Area under the curve
BMI	Body mass index
CA	Cerebral autoregulation
CBF	Cerebral blood flow
CBFv	Cerebral blood flow velocity
CBVC	Cerebrovascular conductance
CBVR	Cerebrovascular resistance
CERT	Consensus on Exercise Reporting Template
CC	Conventional care
COVID-19	Coronavirus Disease 2019
CRF	Cardiorespiratory Fitness
CRP	C-reactive protein
CVD	Cardiovascular disease
CVR	Cerebrovascular CO ₂ reactivity
DBP	Diastolic blood pressure
DAS28	Disease activity score 28
DRE	Dynamic resistance exercise
ENMO	Euclidean Norm Minus One
ERS	Exercise referral scheme
ESR	Erythrocyte sedimentation
EULAR	European League Against Rheumatism
FACIT	Functional assessment of chronic illness therapy – fatigue scale
FMD	Flow-mediated dilation
GLTEQ	Godin Leisure Time Exercise Questionnaire
GP	General Practitioner
HCPs	Healthcare professionals
HDL-C	High density lipoprotein cholesterol
HIIT	High-intensity interval training
HR	Heart rate
HRPAS	Heart rate physical activity score
ICA	Internal carotid artery
IRE	Isometric resistance exercise
LDF	Laser Doppler flowmetry
Li	Low intensity
MAP	Mean arterial pressure
MCID	Minimum clinically important difference
MCA	Middle cerebral artery
MCAv	Middle cerebral artery velocity
MET/METs	Metabolic equivalent(s)
MI	Medium intensity
MICT	Moderate-intensity continuous training

MPA	Moderate physical activity
MVE	Moderate-to-vigorous exercise
MVPA	Moderate-to-vigorous physical activity
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health Care Excellence
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
PA	Physical activity
PHQ-8	Patient health questionnaire depression scale 8
PU/PUs	Perfusion unit(s)
RA	Rheumatoid arthritis
RADAI 5	Rheumatoid arthritis disease activity score 5
RCT/RCTs	Randomised-controlled trial(s)
RF	Rheumatoid factor
RoM	Range of motion exercise
SAEv	Serious adverse events
SB	Sedentary behaviour
SBP	Systolic blood pressure
SD	Standard deviation
S	Sports activities
SF-36	36-Item Short Form Survey
TCD	Transcranial Doppler ultrasound
TFA	Transfer function analysis
TG	Triglycerides
TNF/TNF-a	Tumour necrosis factor(-alpha)
VIT	Vigorous-intensity training
VPA	Vigorous physical activity
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

1.1 Thesis Structure

This thesis is organised into 7 chapters. *Chapter 1* provides a brief introduction and background to the PhD, as well as outlining the primary aims and objectives. *Chapter 2* goes on to provide a critical review of existing literature, as well as providing rationale for the following empirical research study chapters. *Chapters 3, 4, 5 and 6* detail four empirical research studies that form the main body of this thesis. Each research study includes a brief and specific introduction related to the aim of the study, a description of the employed methods, presentation of the results, and a critical discussion of the findings in relation to previous literature. *Chapter 7* synthesises key findings from the PhD and proposes implications of the research and recommendations for future directions.

1.2 Background

There are two major themes within this thesis: physical activity (PA) prescription and cardiovascular risk in people living with rheumatoid arthritis (RA). PA prescription is an important target area for the management of RA due to the fact that individuals with RA present with low levels of PA in comparison with the general population (Lee et al., 2012b, Summers et al., 2019). Additionally, previous literature has also demonstrated that people living with RA have a ~50% increased risk of cardiovascular disease (CVD) compared to the general population (Agca et al., 2017). The CVD risk in RA is not fully explained by specific novel RA risk factors, such as systemic inflammation, with traditional risk factors such as physical inactivity also playing a role (John et al., 2009, Baghdadi et al., 2015, Bordy et al., 2018). PA represents a modifiable CVD risk factor in RA that may benefit both disease symptoms and CVD risk. As such, it is important to assess the latest novel advances in PA prescription for people living with RA in the management of these patients to attempt to positively impact disease specific issues and overall health. To examine the latest advances

in PA prescription, **objective 1** of this thesis is to examine the feasibility and acceptability of a home-based exercise intervention supported by mobile health (mHealth) technology vs. a home-based exercise intervention supported by the provision of virtual exercise resources.

To assess the proposed interventions remote data collection techniques were utilised. This involves participants completing remote testing measurements whereby they will record their own health outcomes from home, allowing for a larger sample of participants (i.e., nationwide). Previous evidence from clinical trials has suggested that the elimination of research facility visits enhances participation for some minority groups that are traditionally underrepresented (Noonan and Simmons, 2021). Although, it is currently unknown whether remote clinical trials are feasible and can provide effective and accurate data collection. As such **objective 2** of this thesis is to examine the feasibility and acceptability of remote data collection.

Following on from **objective 1**, which aims to firstly establish the feasibility and acceptability of a home-based exercise intervention supported by mHealth technology by examining its impact on inactive individuals; the intervention was then adapted to specifically suit the needs of people living with RA. The RA population face common barriers to PA and exercise (e.g., lack of time) but also condition specific barriers such as reduced mobility/functional ability, stiffness, pain and fatigue. Intriguingly, all of these barriers have been shown to significantly improve once people living with RA commence exercising (Metsios and Kitas, 2018), with physically active RA patients exhibiting a higher self-regulatory efficacy to overcome RA specific barriers (Gyurcsik et al., 2013). Accordingly, **objective 3** is to examine whether an RA specific mHealth technology supported intervention can elicit increases in PA levels in people living with RA. Due to the unique barriers to PA faced by people living with RA it is also important to assess the feasibility of

any intervention seeking to upregulate PA. Thus **objective 4** is to assess adherence and compliance to the intervention. Moreover, it is known that PA can have a beneficial effect on disease symptoms and quality of life (UK Chief Medical Officers, 2019, Metsios et al., 2013, Metsios et al., 2020). Therefore, **objective 5** is to investigate the effect of an mHealth technology supported intervention on basic clinical outcomes, quality of life and disease activity.

Cardiovascular risk in people living with RA is a key theme of this thesis due to the association between RA and increased morbidity and mortality as a result of CVD (John et al., 2009). Resultantly, previous studies have explored vascular function in people living with RA which have thus far generated mixed findings. For example, some studies have reported reduced vascular function in people living with RA (Xu et al., 2017) compared to their non-RA counterparts, whilst others have not (Van Doornum et al., 2003). As such, this thesis aimed to further explore vascular function in comparison to matched controls via the concurrent assessment of vascular function across the vasculature tree. Leading to **objectives 6,7 and 8** which are to investigate the impact of RA on; microvascular function by utilising laser Doppler flowmetry (**objective 6**), macrovascular function in the brachial and femoral arteries assessed via FMD (**objective 7**) and cerebrovascular function, specifically cerebral reactivity to CO₂ and cerebral autoregulation (CA), using transcranial Doppler ultrasound (**objective 8**). The assessment of cerebral reactivity to CO₂ and CA in RA is particularly novel and important given emerging evidence of cerebrovascular disease in RA (Wiseman et al., 2016).

There is a growing body of evidence that indicates the significant benefits of structured exercise in RA (Cooney et al., 2011). Though, as previously mentioned PA levels in the RA population are low (Lee et al., 2012b, Summers et al., 2019). A prominent barrier for participation in structured exercise programmes is lack of support and adequate advice

from rheumatology healthcare practitioners (Veldhuijzen van Zanten et al., 2015b) which could be related to the known lack of confidence in prescribing PA and exercise from RA health care professionals (HCPs) (Law et al., 2013, McKenna et al., 2019). One potential reason for this lack of confidence could be poor reporting of exercise interventions which diminishes the ability of HCPs to interpret study findings (Glasziou et al., 2008). Accordingly, **objective 9** of this thesis is to conduct a systematic scoping review summarising the existing exercise interventions utilised in randomised controlled trials involving individuals living with RA. Finally, **objective 10** is to assess the level of reporting of these exercise interventions by applying the Consensus on Exercise Reporting Template (CERT) In the same systematic scoping review.

1.3 Aims

The aims of this thesis are to:

1. Examine the feasibility and acceptability of a home-based exercise and PA intervention supported by mHealth technology vs. a home-based exercise intervention supported by the provision of virtual exercise resources, as well as remote data collection techniques.
2. Examine the effectiveness of an mHealth technology supported intervention to increase PA levels in people living with RA. Also, assessing adherence and compliance to the intervention, and the effect on basic clinical outcomes, quality of life and disease activity.
3. Explore the impact of RA on micro-, macro- and cerebrovascular function in comparison to matched controls via the concurrent assessment of vascular function across the vasculature tree.

4. Conduct a systematic scoping review to summarise existing exercise interventions utilised in randomised controlled trials involving individuals living with RA and to assess the level of reporting of these exercise interventions by applying the CERT.

1.4 Objectives

The aims outline above will be achieved through the following objectives:

To address Aim 1:

1. Develop a home-based exercise and PA intervention to be supported by i) mHealth technology or ii) virtual exercise resources.
2. Develop remote data collection measures to obtain health, physical activity and adherence and compliance data.
3. Assess the feasibility of the home-based exercise and PA interventions by assessing adherence and compliance to each intervention.
4. Assess the acceptability of the home-based exercise and PA interventions via surveys and semi-structured interviews.
5. Assess the feasibility of remote data collections techniques by the comparison of multiple data collection methods, as well as calculating data availability.
6. Assess the acceptability of remote data collections techniques via surveys and semi-structured interviews.

To address Aim 2:

7. Develop an mHealth technology supported intervention to elicit increases in PA levels in people living with RA.
8. Assess feasibility and acceptability of the intervention via measures of adherence and compliance to the mHealth technology supported intervention.

9. Examine the effect of an mHealth technology supported intervention on basic clinical outcomes, quality of life and disease activity.

To address Aim 3:

10. Examine microvascular function in the forearm and calf using laser Doppler flowmetry.
11. Examine macrovascular function in the brachial and femoral arteries using flow-mediated dilation technique.
12. Examine cerebrovascular function, specifically cerebral reactivity to CO₂ and CA, using transcranial Doppler ultrasound.

To address aim 4:

13. Conduct a systematic scoping review summarising the existing exercise interventions utilised in randomised controlled trials involving individuals living with RA.
14. In the same systematic scoping review, assess the level of reporting of these exercise interventions by applying the CERT.

CHAPTER 2: LITERATURE REVIEW

2.1. Rheumatoid Arthritis

2.1.1. A brief introduction to rheumatoid arthritis

RA is a chronic inflammatory autoimmune disease associated with progressive disability, systemic complications, premature death and socioeconomic cost (Firestein, 2003). The latest figures suggest RA affects approximately 0.24% of the world population (Cross et al., 2014), with common characteristics including synovial and systemic inflammation, swelling, tenderness and joint pain, physical incapacity and incidence of several co-morbidities (Gibofsky, 2012). RA can affect individuals of any age, though incidence is increased in people aged over 40 years, additionally females are two to three times more likely to be affected (Scott et al., 2022). There are numerous types of arthritis which can be classified into non-inflammatory (e.g., osteoarthritis), inflammatory arthritis caused by crystal deposits (e.g., gout), bacterial and viral infections (e.g., septic arthritis) or by autoimmune processes as is the case with RA. However, RA is not the only autoimmune rheumatic disease, the group also includes, but is not limited to, systemic lupus erythematosus and Sjögren's syndrome. As such a lot the signs and symptoms of this group of diseases can be the same, highlighting the importance of differential diagnosis (Radu and Bungau, 2021).

2.1.2 Epidemiology

RA is a global disease, distributed worldwide. Prevalence of RA has changed over time and does vary depending on population characteristics/demographics (Safiri et al., 2019). The prevalence (i.e., number of cases) of RA has been rising largely unanimously since 1990 (data up to 2021) (Radu and Bungau, 2021). At present the global prevalence of RA is around 0.24% (Cross et al., 2014), with most studies reporting a three-to-five-fold higher prevalence in females, compared with males (Radu and Bungau, 2021). Incidence (i.e. number of new cases) of RA varies by age and population. The most recent research has

reported that Ireland has the highest age-standardised incidence rate (30.03 per 100,000 people), whilst the same number has reduced in the UK by 0.14% (Cai et al., 2023). The reasons for changes in incidence rates cannot be fully explained, but there are likely to be risk factors related to environmental factors that play a role (Gibofsky, 2012, Radu and Bungau, 2021). For example, recent research has suggested that the COVID-19 pandemic resulted in a 40% fall in incidence rates during the early stages of the pandemic, despite there being no evidence that rheumatology assessments times were affected (Russell et al., 2022). However, it has also been suggested that incidence rates have risen post-pandemic, with the greatest increase occurring before the first-year post-pandemic (Marín et al., 2023).

2.1.3. A brief pathophysiology of RA

The exact pathogenesis of RA is complicated not completely understood, involving different components of the immune system (Alivernini et al., 2022, Petrelli et al., 2022). The leading hypothesis for RA is that genetic susceptibility, epigenetic modifications and the interaction of environmental *triggers* leads to altered post-transcriptional regulation and self-protein citrullination early in the disease process (Gibofsky, 2012, McInnes and Schett, 2011). Recent progress in genotyping technology has led to the discovery of multiple alleles being associated with increased risk of RA, in particular the HLA-DRB1 gene (Petrelli et al., 2022). This *susceptibility* gene, along with HLA-DR4, causes the body's immune system to be unable to recognise citrullinated proteins (e.g., type II collagen, vimentin) as self-structures (Van Drongelen and Holoshitz, 2017). This leads to the development of anti-citrullinated protein autoantibodies (ACPAs), resulting in loss of tolerance to self (McInnes and Schett, 2011). The presence of RF also signified autoantibody production (McInnes and Schett, 2011), this systemic antibody production and resulting inflammation can occur for up to 15 years before meeting the clinical criteria for RA diagnosis (Isaacs, 2010).

The transition to RA then occurs via several mechanisms that are not well understood, such as infectious triggers and neuroimmune factors (McInnes and Schett, 2011). Synovitis is then perpetuated by the adaptive and innate immune pathways, along with cytokines, growth factors and intracellular signalling molecules. It is this genetic variation of the immune system in people with RA that leads to the immunity and destruction (Gibofsky, 2012). A variety of inflammatory cell types are able to penetrate the synovial membrane and work to ultimately cause the destruction of the joint (McInnes and Schett, 2011). The burden of RA also extends beyond the joints and pain, there are also extra-articular manifestations and systemic complications relating to the disease process (Gibofsky, 2012). For instance, cardiovascular complications are very common in RA, with the majority of deaths in members of this clinical group being related to cardiovascular disease (CVD) (McInnes and Schett, 2011, Kitas and Gabriel, 2011). This highlights the need to focus on the systemic complications of RA, with CVD at the forefront.

2.1.4. RA risk factors

It has been suggested that RA may be caused by genetic and environmental factors (Roberts-Thomson et al., 2002), with the greatest risk coming from genetics at an estimated 50% (Petrovská et al., 2021). It is important to note there are two types of RA: Seropositive RA (presence of rheumatoid factor [RF] and/or ACPAs) and seronegative RA (neither RF or ACPAs present), both of which carry different risk factors related to specific alleles and genes. Environmental risk factors play a role, for example smoking is associated with an increased risk of RA (Vessey et al., 1987) but is likely to affect incidence of seropositive RA, and not seronegative RA (Ishikawa and Terao, 2020, Linn-Rasker et al., 2005). Another example is dietary factors, with suggestions that consumption of red meat is associated with early onset RA (Jin et al., 2021). Pregnancy and infections, such as Epstein-Barr virus, have also been reported as risk factors for RA (Kobayashi et al., 2008).

Overall, there have been multiple genetic and environmental factors associated with RA proposed. The strongest being familial association and first-degree relative status, though it's unclear whether this always falls under genetic factors or could be linked to environmental factors too (Deane et al., 2017). These risk factors need to be assessed further to identify individuals who may be at a higher risk of RA, which may allow for preventative strategies and interventions to be utilised in the future.

2.1.5. Symptoms and diagnosis

RA is primarily diagnosed on physical examination findings with the use of two classification criteria. The first of which, published in 1987, has been criticised for focusing on identifying more established RA disease (Arnett et al., 1988). As such the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) created a classification for identification earlier in the disease process (Aletaha et al., 2010), where the most benefit can be gained from treatment. Thus, it has been recommended that the 2010 ACR/EULAR criteria should now be used for the assessment of new and existing patients to facilitate earlier administration of treatments capable of positively influencing disease progression.

Table 2.1. Comparison of historical and current RA classification criteria.

Criteria	1987 Criteria		2010 Criteria	
	Description	Score	Description	Score
Morning stiffness	In and around joints, for at least 1 hour	1	Clinical synovitis/swelling in at least 1 joint not explained by another disease	N/A
Joint involvement	Physician observed soft tissue swelling or fluid in 3 of 14 possible joints	1	1 large joint	0
			2-10 large joints	1
			1-3 small joints (with or without large joint)	2
			4-10 small joints (with or without large joint)	3
			> 10 joints (at least 1 small)	5
Arthritis of hand joints	At least 1 swollen hand or wrist area	1	N/A	N/A
Symmetric arthritis	Simultaneous bilateral involvement	1	N/A	N/A
Rheumatoid nodules	Subcutaneous nodules over bony prominences, extensor surfaces, or in juxta articular regions observed by physician	1	N/A	N/A
Serology	Positive RF serum test	1	Negative RF and negative ACPA	0
			Low-positive RF or ACPA	2
			High-positive RF or ACPA	3
Radiographic changes	Erosions of unequivocal bony decalcification in or adjacent to the involved joints, but not consistent with osteoarthritis	1	N/A	N/A
Acute phase reactants	CRP and ESR	N/A	Normal CRP and ESR	0
			Abnormal CRP or ESR	1
Duration of symptoms	First four criteria present for ≥ 6 weeks	N/A	< 6 weeks	0
			≥ 6 weeks	1
Criteria score required		$\geq 4/7$		$\geq 6/10$

Acronyms: ACPA; anti-citrullinated protein antibody, CRP; C-reactive protein, ESR; erythrocyte sedimentation rate, NA; not applicable, RF; rheumatoid factor.

2.1.6. Treatment

Though the definitive cause of RA is still unknown, increased understanding of the pathogenesis of the disease has led to the development of new therapeutics that has led to improved outcomes (McInnes and Schett, 2011). The primary objectives of treatment for RA are to reduce joint inflammation and pain, maximise joint function and prevent joint destruction and deformity. Treatment is generally customised to a patient's needs and overall health, though it usually combines pharmaceuticals, non-pharmaceuticals (e.g., weight bearing exercise), education and rest (Bullock et al., 2019). The current treatment strategy employed is to commence aggressive therapy soon after diagnosis and escalate, as required, with the goal of achieving clinical remission (McInnes and Schett, 2011). This aggressive, proactive approach is required due to the fluctuant nature of RA, with episodic flares occurring in the absence of optimal treatment, which leads to worsened symptoms that can ultimately cause irreversible joint damage, affecting both physical and psychological functioning (Radu and Bungau, 2021). In addition, RA complications and comorbidities can reduce life expectancy (Lassere et al., 2013), highlighting the necessity to diagnose and treat RA as efficiently as possible.

The most effective approach to date is early diagnosis followed by both optimal nonpharmacological and pharmacological treatment, combined with recurring evaluation of treatment efficacy and safety (Radu and Bungau, 2021). According to the latest guidance (National Institute for Health Care Excellence, 2018b), first-line treatment utilises conventional disease-modifying anti-rheumatic drugs (cDMARDs), such as oral methotrexate, leflunomide or sulfasalazine, and is ideally started within 3 months of symptoms. A bridging treatment (glucocorticoids) is also sometimes used when starting cDMARDs. The dose is then escalated (as tolerated), with hydroxychloroquine sometimes used as an alternative to the aforementioned cDMARDs for mild or palindromic disease. If

the treatment target is not reached after escalation, a combination of CDMARDs may be used. Glucocorticoids are also sometimes used to manage flares during treatment but are not usually used over a long-term period. Furthermore, to control symptoms non-steroidal anti-inflammatory drugs (NSAIDs) can be used to help control pain and stiffness, however, guidelines suggest offering the lowest effective dose for the shortest possible time.

People with RA can also benefit from non-pharmacological treatment such as physical and occupational therapy. Specifically, regular exercise, joint mobility and strengthening of the muscles around joints is recommended (Osthoff et al., 2018). However, despite these recommendations and evidence confirming the positive impact of PA and exercise in RA (Katz et al., 2020, Metsios and Kitas, 2018), engagement in PA and exercise remains low within the RA population (Summers et al., 2019). This may be due to uncertain PA and exercise advice provided to RA patients by their healthcare team (Halls et al., 2017), stemming from rheumatologist's significant knowledge gaps on PA (Astley et al., 2021). Therefore, in terms of RA treatment, non-pharmacological approaches such as PA and exercise warrant further investigation in order to maximise the benefits that can be achieved through prescription of this type of treatment in conjunction with pharmaceutical therapies.

2.2. Rheumatoid Arthritis and Cardiovascular Disease

2.2.1. The relationship between rheumatoid arthritis and cardiovascular disease

RA is associated with an increased morbidity and mortality as a result of CVD, mostly accelerated atherosclerotic CVD (John et al., 2009). Addressing the co-morbidities associated with RA, such as CVD, is a large part of the clinical management required for people living with RA, alongside managing the inflammatory joint disease itself. People living with RA are known to die prematurely (Alamanos et al., 2006), with this increased risk of mortality owing largely to higher rates of CVD related death (Aviña-Zubieta et al.,

2008). This is reflected in previous research has reported that people with RA have a two-fold risk of myocardial infarction and up to a 50% increased risk of CVD mortality when compared with the general population (Choy et al., 2014, Agca et al., 2017)

The increased risk of CVD in people living with RA has been attributed to the interplay between traditional cardiovascular risk factors, which could be adversely affected by RA, as well as RA specific factors such as systemic inflammation (John et al., 2009, Baghdadi et al., 2015, Bordy et al., 2018) leading to alterations in vascular structure and function that may promote atherosclerosis, as depicted in Figure 2.1. (Skeoch and Bruce, 2015).

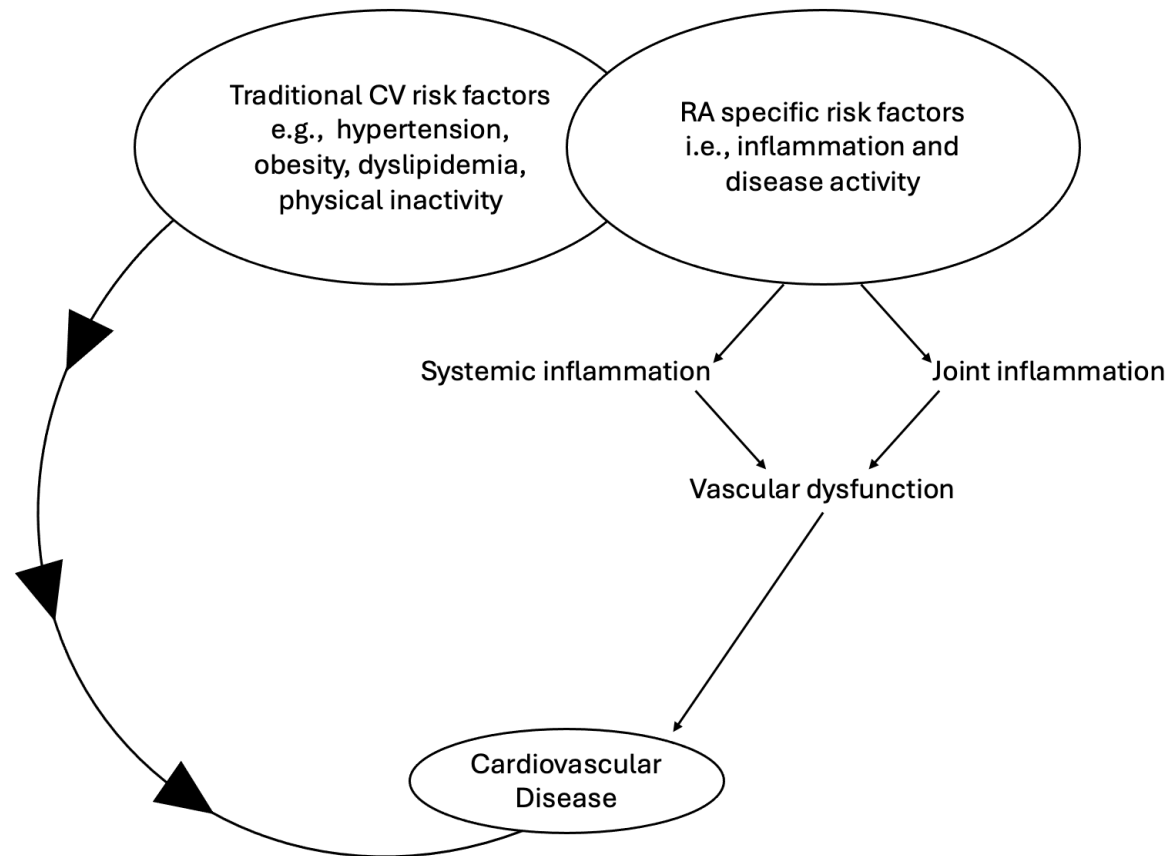


Figure 2.1. A schematic illustration of the impact of traditional and RA specific risk factors for cardiovascular disease.

2.2.1.1. The role of traditional cardiovascular risk factors

Traditional CVD risk factors, including but not limited to hypertension, dyslipidaemia and obesity, are highly prevalent in people living with RA (Liao and Solomon, 2013, Baghdadi et al., 2015). Hypertension, for example, is a modifiable CVD risk factor that is common amongst people living with RA (Hitchon et al., 2016, Chen et al., 2018). (Hitchon et al., 2016, Chen et al., 2018). Moreover, it has been suggested that factors related to RA such as systemic inflammation, physical inactivity, diet and alcohol contribute to higher rates and poorer control of hypertension in people living with RA (Panoulas et al., 2008, Jagpal and Navarro-Millán, 2018). Similar suggestions of RA related factors having negative effects of traditional CVD risk factors are common, such as alterations to lipid profiles (e.g. lower levels of high-density lipoprotein) due to high-grade inflammation relating to dyslipidaemia in people living with RA (Park et al., 1999, Yan et al., 2023). Another example includes pro-inflammatory cytokines mediating the development of rheumatoid cachexia, which can lead to higher body fat and possibility obesity, thus contributing to CVD risk (Masuko, 2014). Physical inactivity, another traditional CVD risk factor, is irrefutably high in people living with RA especially if they have uncontrolled disease or damaged joints (Sokka et al., 2008)

A narrative review by Liao and Solomon (2013) demonstrated through synthesising previous research that the inflammation and treatment associated with RA can modify the level of CVD risk and change how it is conferred in comparison to the general population. As such, the same review suggests that to accurately describe CV risk in RA, it must be considered how RA (particularly inflammation) may modify traditional risk factors, as opposed to viewing the two independent of one another. However, the notion that traditional CVD risk factors can be manipulated differently in people living with RA, suggests that these factors alone are likely to underestimate CVD risk in RA (Kitas and Gabriel,

2011), potentially by five-fold (Crowson et al., 2009). Consequently, it is likely that novel RA specific factors also play a key role in the increased risk of CVD in RA.

2.2.1.2. The role of rheumatoid arthritis specific cardiovascular risk factors

RA specific cardiovascular risk factors are likely to relate to the vascular and metabolic effects of systemic inflammation. It has been suggested that atherosclerosis itself is a chronic inflammatory disease of large and medium-sized arteries that causes CVD events such as ischemic heart disease and strokes (Kobiyama and Ley, 2018, Skeoch and Bruce, 2015), both of which are more likely in the RA population (Rezuş et al., 2021, Holmqvist et al., 2013). Endothelial dysfunction is the first stage of atherosclerosis, when this occurs the expression of proinflammatory cytokines and cellular adhesion molecules is increased (Anderson, 1999). This causes the endothelium to become permeable and allow the entry of inflammatory cells and lipid molecules (Skeoch and Bruce, 2015) causing high levels of low-density lipoprotein in the subendothelial layer, leading to the formation of fatty streaks (foam cells and T-lymphocytes and migrated smooth muscles cells) leading to intima-media thickening which then progresses to intermediate and advanced lesions that develop a fibrous cap forming plaque, thus potentially occluding the arterial lumen (Ross, 1999, Kobiyama and Ley, 2018). As plaques grow more complex, the fibrous cap begins to thin (Sakakura et al., 2013) leading to rupture and clinical events. It is now accepted that inflammation plays a significant role in the development and stability of the aforementioned lesions (Skeoch and Bruce, 2015) and is a trigger for plaque erosion and volatility to rupture, leading to the development of anti-inflammatories for plaque stabilisation (Everett et al., 2013).

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Figure 2.2. A schematic illustration of the development of atherosclerosis and pathological characteristics of different types of atherosclerotic plaques. (a) The four stages of pathological progression of atherosclerosis. (b) The vulnerable plaque (bottom right) has a high risk for rupture and thrombosis, composed of a lipid-rich necrotic core, inflammatory cells and cytokines, thin fibrous cap, and neovascularization, compared with stable plaque (top left) (Zhang et al., 2022).

Modest increases in circulating c-reactive protein (CRP), that depict low-grade systemic inflammation, have been associated with CVD risk (Casas et al., 2008, Collaboration, 2010). Thus, the idea that the high-grade systemic inflammation seen in RA may contribute to increasing CVD risk is plausible. Moreover, similar pathophysiological mechanisms (i.e., chronic and systemic inflammation) shared between RA, CVD and secondary accelerated atherosclerosis have been shown consistently (Gremese and Ferraccioli, 2011). Thus, it has been postulated that the high-grade systemic inflammation observed in RA plays a pivotal role in the accelerated atherosclerosis in these patients (Goodson et al., 2005). Atherosclerosis is more prevalent in RA than the general population, with lesions progressing faster and possibly more susceptible to rupture (Giles et al., 2011). As well as higher plaque burden, increased prevalence of high-risk lesions (associated with high disease activity) have been identified in people living with RA compared to the general population (Karpouzas et al., 2014). This highlights a possible association between

inflammatory burden and high-risk plaque formation (Skeoch and Bruce, 2015). In addition to inflammation, RA specific autoantibodies such as rheumatoid factor and ACPAs have been associated with CVD (Cambridge et al., 2013). As has Periodontitis, which is associated with higher presence of ACPAs even in those without RA and is linked to increase risk of CVD (Bahekar et al., 2007).

2.2.1.3. The relationship of shared risk factors in rheumatoid arthritis and cardiovascular disease.

RA and CVD have a myriad of shared risk factors that could promote both conditions (Skeoch and Bruce, 2015). These include shared genetic risk factors (e.g. HLA-DRB1), traditional CVD risk factors and novel RA specific risk factors. For example, the evidence presented above clearly indicates a relationship between increased CVD risk, RA and inflammation. Given this body of evidence there are recommendations to make sure people living with RA are screened for traditional CVD risk factors and to provide an appropriate care pathway where necessary, whilst also effectively controlling inflammation levels (Skeoch and Bruce, 2015). Thus, approaching both traditional and novel RA specific CVD risk factors together, would have the best possible impact on reducing CVD risk (Liao and Solomon, 2013, Skeoch and Bruce, 2015).

2.2.1.4. The effect of treatment on CVD risk factors in rheumatoid arthritis.

Despite the widely utilised approach to treatment of CVD risk factors in people living with RA there is currently little information on the management of traditional CVD risk factors in the population (Skeoch and Bruce, 2015). Contrastingly, management and treatment of inflammation within people living with RA is a longer standing component of management of the disease and thus is well researched. Therefore, it is possible that the controlling of inflammation via RA specific treatment may also allude to reductions in CVD risk via the same pathway of controlling inflammation. However, it must be noted that there is no

evidence to suggest cardiovascular mortality rates are falling more in people living with RA compared to the wider general population, with a large mortality gap remaining (Brown et al., 2006, Johnson et al., 2023). A potential explanation for this is the possible persistence of low-grade inflammation in people living with RA that may continue to drive atherosclerosis (Skeoch and Bruce, 2015). Pharmacological treatments may have a positive effect on CVD risk as well as RA disease symptoms. For example, methotrexate use has been associated with a decrease in cardiovascular risk via reductions in systemic inflammation, though the mechanisms involved are only partially identified and effects on endothelial function and atherosclerosis remain contentious (Verhoeven et al., 2021). Furthermore, modern biological treatments such as anti-tumour necrosis factor (TNF) therapy have also been associated with a reduction in CVD risk in people living with RA (Solomon et al., 2013). It is possible that specific RA treatments may also have a beneficial effect on CVD risk, however, more research is required to better understand RA specific CVD pathways in order to maximise the potential of treatment plans to combat both RA and CVD risk.

2.2.2. Rheumatoid arthritis and vascular structure and function

It is no surprise that vascular structure and function has been confirmed to be impaired in people living with RA compared to non-RA controls (Sandoo et al., 2011b). As previously mentioned, it has been suggested that the systemic inflammation present in RA may lead to pro-inflammatory molecules causing a negative effect on the vascular endothelium (Sandoo et al., 2011b), leading to reduced nitric oxide (NO) synthase and thus endothelial dysfunction (Clapp et al., 2004). This is important as inflammation may be having a direct effect on the vasculature potentially leading to increased CVD risk, as well as having the same effect through enhancing traditional CVD risk factors. Vitally, endothelial dysfunction can occur with any apparent clinical symptoms (Gonzalez and Selwyn, 2003), meaning that

finding novel ways to assess vascular function to detect dysfunction at an early stage is vital in populations where CVD risk is high (Metsios et al., 2010).

2.2.2.1. Microvasculature

Also known as the microcirculation, the microvasculature's primary function is to guarantee adequate oxygen and nutrient delivery to meet the metabolic demands of organ cells and to remove their waste products (Gutterman et al., 2016). The microvasculature consists of three types of small vessels: arterioles, capillaries and venules, which form a network that regulates local blood perfusion and conducts blood-tissue exchange (Levick, 2013). Blood flow to capillaries is supplied by arterioles that are surrounded by vascular smooth muscle. Blood entering the capillary bed is controlled by the vasodilation/vasocontraction of arterioles and precapillary sphincters. Humoral factors (e.g., angiotensin) and metabolic factors (e.g., NO) dictate vasodilation/vasocontraction to meet the metabolic demands of tissues. Blood then flows into the capillaries and is carried out to the venous circulation by postcapillary venules. Blood can also be shunted directly from the arterioles to the venules via metarterioles, bypassing the capillary bed. These mechanisms control the hydrodynamic pressure and volume of blood flow through individual capillary beds to meet the metabolic and respiratory demands of the tissues.

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Figure 2.3. Architecture of a microvascular bed. (Yuan et al., 2011)

Importantly for people living with RA, the microvasculature also controls inflammation, acting as the entry point for inflammatory cells to enter tissues (Bordy et al., 2018). Despite, macrovascular function being researched in greater detail to this point, the microvasculature offers the chance to potentially detect dysfunction earlier as it is known that microvascular endothelial dysfunction precedes and predicts conduit artery atherosclerosis (Gutterman et al., 2016). As such, microvascular endothelial dysfunction has been referred to as '*a warning signal*' preceding conduit artery atherosclerosis (Bordy et al., 2018).

There is an abundance of evidence demonstrating that microvascular endothelial function is impaired in people living with established RA for ≥ 12 (Bordy et al., 2018). This has been determined by assessing microvasculature in the skin (Arosio et al., 2007), brachial (Yki-Järvinen et al., 2003) and coronary microvasculature (Ciftci et al., 2008). Though it should be noted, despite limitations such as mixed cohorts, differing methods of assessment and presence of other co-morbidities, other studies have not found microvascular endothelial dysfunction (Foster et al., 2010, Santos et al., 2012, Bordy et al., 2018). At present no

definitive conclusions can be made on the link between inflammation in RA and microvascular endothelial dysfunction, owing to the numerous limitations within the current evidence (Bordy et al., 2018). Thus, more research is warranted to build upon the current evidence to better understand microvascular dysfunction in RA, especially assessing function at different locations (i.e., forearm and calf) as well as a future focus on the mechanisms of microvascular endothelial dysfunction in people living with RA.

The method of assessment of the microvasculature used in this thesis is laser Doppler flowmetry (LDF). LDF is a non-invasive technique that allows for the estimation of microcirculatory blood flow (Nilsson et al., 1980). In brief, it utilises Doppler shift that occurs when light is scattered by moving particles, in this case red blood cells (RBCs). A perfusion estimate (that increases with both the tissue fraction of RBCs and RBC flow) is garnered from calculating the first moment of the detected Doppler power spectrum (Nilsson et al., 1980). The tissue fraction of moving RBCs is estimated by calculating the zero-order moment of the Doppler power spectrum. Then normalising the perfusion by RBC tissue fraction provides an estimate of average blood flow speed (Fredriksson et al., 2010). LDF is unique in that it can assess microcirculation non-invasively, but it is highly affected by tissue optical properties and structure at the measurement site (Larsson et al., 2002). The cutaneous RBC flux is expressed in perfusion units (PUs) and reflects local cutaneous blood flow from the Doppler probe place on the skin. Changes in cutaneous blood flow are expressed as cutaneous vascular conductance (CVC) which is defined as flux divided by mean arterial pressure (MAP) and is expressed as PU/mmHg (Cracowski et al., 2006). This is a useful tool in assessing microvascular function in an accessible, non-invasive manner, that may allow for the early detection of vascular dysfunction acting as a warning sign for atherosclerosis (Bordy et al., 2018).

2.2.2.2. Macrovasculature

Macrovasculature refers to any of the large blood vessels within the body, including the arteries and veins which transport blood rapidly toward or from organs. The entire circulatory system has an inner lining of a single layer of cells known as the endothelium. The endothelium is located between the vessel wall and circulating blood, and responds to changes in its physical, chemical or humoral environment (Rubanyi, 1993). Moreover, NO is constantly produced by the endothelium at a low basal rate which maintains vessel health and regulates vascular tone. NO is a powerful vasodilator and anti-atherogenic molecule (Green et al., 2011). Increases in blood flow cause increase intimal shear stress (frictional drag of blood flow on the arterial wall) which is a physiological stimulus for the release of NO, causing vasodilation. Flow-mediated dilation (FMD), the technique used to assess macrovascular function in this thesis is a largely NO mediate dependent test of endothelial function (Thijssen et al., 2011). FMD is commonly used technique and is a predictor of cardiovascular events in both those with established CVD and asymptomatic subjects (Thijssen et al., 2011). As such, FMD is an incredibly useful tool to identify individuals who may be at an increased risk of future cardiovascular events. It is conducted by imposing an increase in blood flow and shear stress in a conduit artery, that is achieved via rapid cuff occlusion, whilst using vascular ultrasound to image the artery (Thijssen et al., 2019).

People living with RA are known to have a high prevalence of macrovascular disease, this can take various forms including: carotid artery disease, peripheral artery obstructive disease and subclinical heart disease (Alkaabi et al., 2003a). Moreover, previous research has demonstrated that people living with RA presented with greater carotid average intima-media thickness (Alkaabi et al., 2003a) which has been linked with increased risk of stroke and MI in older adults (O'leary et al., 1999). It is well known that the RA population

has increased cardiovascular mortality which may be related to endothelial dysfunction, this has been shown in studies that have observed changes in macrovascular reactivity. This includes reduced FMD and increased arterial stiffness (Xu et al., 2017, Di Minno et al., 2015, Wållberg-Jonsson et al., 2008), however other research has not found any differences in FMD between RA and non-RA counterparts (Van Doornum et al., 2003). The contribution of RA disease activity as well as traditional CVD risk factors to the reduction in FMD seen in some research studies is not clear and requires future investigation.

Another area which requires future examination is the assessment of macrovascular function using FMD in lesser investigated beds such as the femoral artery. Lower limb vascular function studies in people living with RA are scarce. This is despite the fact that the macrovasculature in the lower limbs has been observed to be more susceptible to the development of atherosclerosis. For example, Vink et al. (2002) found that atherosclerosis and intimal thickening were more common in coronary and lower limb arteries (e.g., iliac and femoral arteries) than in the brachial artery during post-mortem assessments of elderly people. In addition it has been suggested that lower limb vascular dysfunction may preceded that of the upper limbs (Sanada et al., 2005). Thus, it is important for future research to examine lower limb macrovascular function alongside the upper limbs, in order to gain a greater understanding of overall vascular health.

2.2.2.3. Cerebrovasculature

To maintain normal function, the brain requires constant adequate nutritional flow supplied via the cerebrovasculature. The internal carotid (ICA) supplies ~70% of total cerebral blood flow (CBF), with the remainder supplied with the vertebral arteries (Willie et al., 2014). The ICA forms the anterior cerebral artery (ACA) and middle cerebral artery (MCA) at the base of the brain, and these branches transport blood throughout the brain

via smaller stem and cortical branches which feed smaller arterioles before feeding into the anterior cerebral capillary beds arteries (Ren et al., 2015). The cerebral vasculature is joined together in multiple locations, forming a structure commonly known as the *Circle of Willis*, connecting the anterior and posterior circulations (Ren et al., 2015). The brain possesses a high metabolic demand, receiving ~25% of total oxygen and ~15-20% of total cardiac output at rest (Folino, 2007). As such, CBF is highly regulated, especially given the limited ability of the brain to store energy (Peters et al., 2004). Cerebral perfusion pressure (CPP), the difference between blood pressure and intracranial pressure, and cerebrovascular resistance, the resistant forces (i.e., increased vascular tone) acting on blood flow through the brain, together determine CBF (Ainslie and Duffin, 2009, Tzeng and Ainslie, 2014).

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Figure 2.4. Architecture of the cerebrovasculature (www.lecturio.com, 2024).

There is not an abundance of research examining the cerebrovasculature in RA, despite it being reported that RA patients have a 30% increased risk of stroke compared to the general population (Lindhardsen et al., 2012). However it appears this is becoming an increasingly investigated area, with emerging evidence surrounding cerebrovascular disease in RA (Wiseman et al., 2016). Though vital mechanisms of cerebrovascular control such as cerebral autoregulation, are yet to be discerned in people living with RA despite it being attenuated in other clinical populations (Van Halm et al., 2009). Thus, it is important to examine any potential impact of RA on cerebrovascular function.

2.2.2.3.1. Transcranial Doppler ultrasound

Transcranial Doppler ultrasound (TCD) is a high temporal resolution, non-invasive technique utilised to measure the functional status of the cerebral blood vessels. It provides feedback on cerebral blood flow velocity (CBFv; $\text{cm}\cdot\text{s}^{-1}$) (Willie et al., 2011). In

order to do so, pulsed ultrasound waves are emitted from a Doppler probe (2 MHz) through the temporal region of the cranium to assess the vessel of interest. CBFv is derived from Doppler shift, where ultrasound waves are reflected from moving erythrocytes within the vessel back to the Doppler probe. The difference between the transmitted and received ultrasound waves provide velocity values, with faster erythrocyte movement being associated with higher velocity (Aaslid, 1986). CBFv has been deemed a reliable surrogate for absolute CBF providing the insonated artery diameter remains constant (Ainslie and Hoiland, 2014). TCD can assess multiple vessels including but not limited to the ACA and MCA, vessel identification is achieved through knowledge of anatomical structure (Willie et al., 2011) and understanding of insonation depths and flow direction of the vessels. The MCA is commonly used to examine CBF as it accounts for ~80% of CBF and is optimally positioned close to the temporal window (Skow et al., 2013). The MCA usually runs laterally and slightly anteriorly after bifurcating from the ICA (Willie et al., 2011). As such it is best insonated from an anterior temporal window providing a near zero insonation angle. The depth of the MCA is typically between 25mm and 50mm, and the flow should be towards the probe [depicted as a red signal as seen in Figure 2.4] with a typical mean CBFv of 55 ± 12 cm.s (Willie et al., 2011). The MCA/ACA bifurcation is often used as an anatomical landmark to standardise a within subject measurement point [Figure 2.4] (Willie et al., 2011).

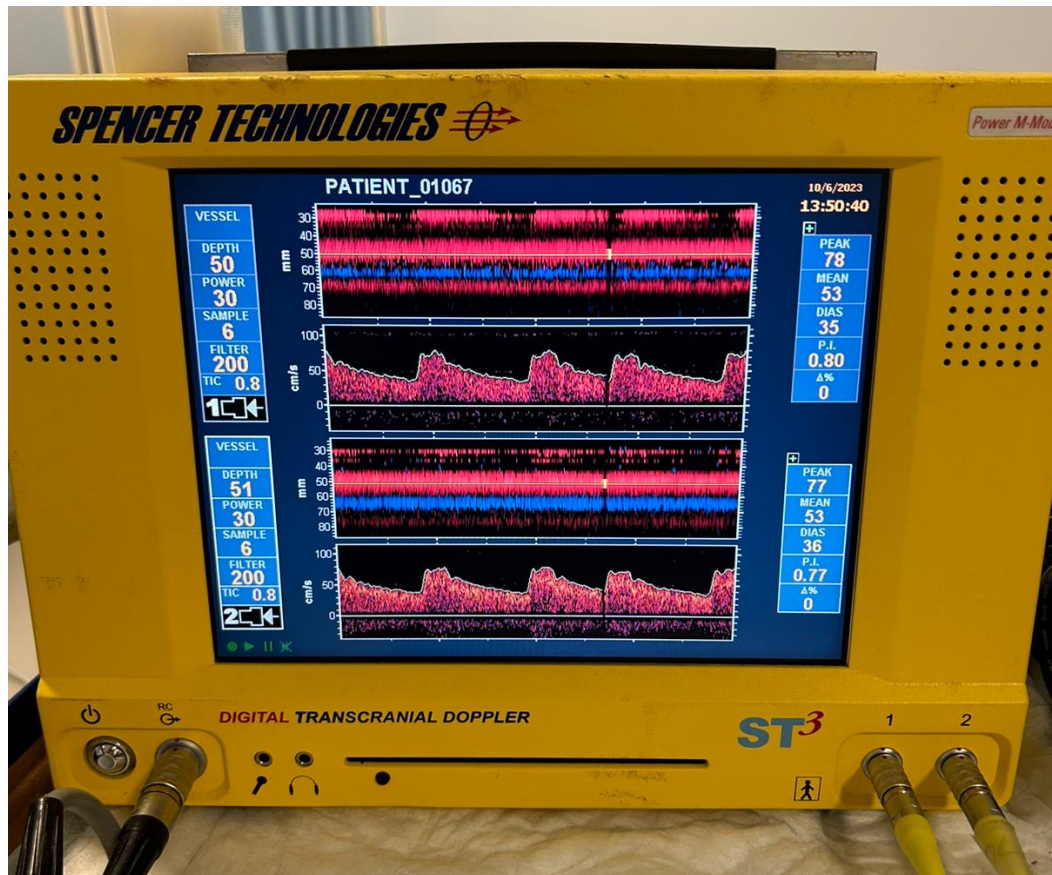


Figure 2.5. An example of a TCD read out taken during the research study in *Chapter 5*.

2.2.2.3.2. A brief overview of the regulation of CBF

CBF regulation is a complex process involving several different mechanisms which include; chemical control (cerebrovascular reactivity) and blood pressure [BP] (cerebral autoregulation) which will be examined in this thesis, as well as cerebral metabolism (neurovascular coupling) and the autonomic nervous system (Willie et al., 2011, Willie et al., 2012, Willie et al., 2014).

2.2.2.3.2.1. Chemical control: cerebrovascular reactivity

CBF is significantly impacted by the partial pressure of arterial carbon dioxide (PaCO_2). Increased PaCO_2 (hypercapnia) causes cerebral arteriolar vasodilation, whilst a decrease (hypocapnia) causes vasoconstriction, reducing CBF (Ainslie and Duffin, 2009). Cerebrovascular CO_2 reactivity (CVR) is the term often used for the sensitive relationship

between changes in PaCO₂ and the CBF response. It reflects the ability of the cerebral vessels to dilate or constrict in response to changes in arterial blood gas content. An increase in CBF as a result of increased PaCO₂ can be viewed as a *defence mechanism* to normalise and/or reduce the rise in PaCO₂ and removed CO₂ from the brain tissue. At rest the cerebrovasculature is more sensitive to rises in PaCO₂ (3-6% increase per mmHg in PaCO₂ above rest) than it is compared to a decrease (1-3% reduction per mmHg) (Willie et al., 2012). This has also been suggested as a protective mechanism to avoid cerebral ischemia during reductions in PaCO₂, which may occur during instances such a posture change (Ainslie and Duffin, 2009).

It has been suggested that CVR is a control mechanism for respiration induced changes in CO₂. Previous research examining responses to a 5% CO₂ stimulus demonstrated that reduced CVR is associated with increased risk of all-cause death (Portegies et al., 2014). The mechanisms behind CVR are equivocal and not fully identified. Suggested mechanisms include; NO and prostaglandins leading to hypercapnic induced vasodilation via increased shear stress (Ainslie and Duffin, 2009, Hoiland et al., 2017) and the activation of potassium channels in the vascular smooth muscle leading to cerebral vessel dilation (Ainslie and Duffin, 2009).

CVR has previously been assessed in different ways. Including the use of a breath hold technique, using a rebreathing technique and another, which is employed in this thesis, using external CO₂ supplied by a non-rebreathing face mask (Fierstra et al., 2013) utilising a standardised hypercapnic stimulus (Vernieri et al., 2004)

2.2.2.3.2.2. Cerebral autoregulation

The brain is able to maintain a relatively constant supply of blood flow despite fluctuations in BP, this phenomenon is termed CA. CA can be classed as another protective mechanism

as it acts to protect the brain against injury from hypo- or hyperperfusion (Novak et al., 1998). An historic paper from Lassen (1959) identified that CBF plateaued across a wide range of BPs (60-150mmHg), though more recent research has demonstrated that this plateau may not exist to such a wide ranging extent of BPs with evidence suggesting a 0.82% change in CBF for every 1 mmHg change in BP (Lucas et al., 2010). Thus, a smaller range ($\pm$ 5-10 mmHg from baseline) as been suggested (Tan, 2012).

There are two types of CA, static cerebral autoregulation (sCA) referring to responses to BP changes across a longer time period (i.e., minutes) and dynamic cerebral autoregulation (dCA) referring to responses to acute BP changes (Tiecks et al., 1995). dCA, as assessed within this thesis, allows for the assessment of CA that best reflects BP oscillations experienced during daily tasks. dCA is measured via monitoring changes in CBFv and MAP on a beat-to-beat basis.

Increases in BP cause vasoconstriction of the cerebral vessels, with decreases in BP resulting in vasodilation of the cerebral vessels, this allows for the maintenance of adequate CBF across a wide range of BP fluctuations (Pires et al., 2013). This is often termed, cerebrovascular resistance, which interestingly has been shown to be more effective at maintaining CBF during periods of increase BP as opposed to decrease, though this difference is attenuated when controlling for PACO₂ (Numan et al., 2014). The underlying mechanisms of CA have not been identified, whilst it is likely they are multifactorial (Tzeng and Ainslie, 2014). Moreover, impaired CA could lead to heightened sensitivity to BP changes, with the failure of CA being associated with increased morbidity and mortality (Hu et al., 2008). Mechanisms specific to dCA are believed to be dependent on the frequency in which changes in arterial BP occur. Low frequency (0.07-0.20Hz), as assessed in this thesis, changes are believed to be controlled by sympathetic influences (Ogawa et al., 2010), whereas myogenic influences may effect very low frequency dCA

(Hamner et al., 2012) and respiration rate may control high frequency dCA (Reinhard et al., 2003). However, significant further research is required to enhance understanding of the relationship between mechanisms controlling CA.

The assessment of dCA is often undertaken using TCD and finger photoplethysmography, allowing for the examination of the response between CBFv and BP as transient changes in BP are induced. The most recent technique to induce these BP changes in order to assess dCA is via squat-to-stand manoeuvres, which are utilised in this thesis, which is now preferred over the previous technique of using bilateral thigh cuffs due to less discomfort (Lipsitz et al., 2000). This technique has been shown to represent BP fluctuations seen in daily life (Simpson and Claassen, 2018), making it ecologically valid, and as such has been used in a variety of research with trained, clinical and elderly populations (Claassen et al., 2009b, Lewis et al., 2019, Labrecque et al., 2021). Other techniques such as sit-to-stands, passive leg raising and respiratory-induced oscillations have also been used in previous research (Brassard et al., 2023).

2.2.2.3.2.3. Transfer function analysis

Transfer function analysis (TFA), a frequency-domain analysis technique, is one of the most common approaches taken to quantify dCA (Claassen et al., 2016, Brassard et al., 2023). In brief TFA estimates metrics that reflect the dynamic behaviour of CA with the assumption that CA is linear (Claassen et al., 2016). TFA metrics include, coherence; the fraction of MAP which is linearly related to CBFv, gain; the amplitude of CBFv change for given changes in MAP and phase; the time difference between MAP and CBFv waveforms (Claassen et al., 2016). It should be noted that there is some debate around the linearity of dCA (Claassen et al., 2016) though recent evidence has argued against the relationship between MAP and CBFv being non-linear (Porta et al., 2020) thus supporting the use of TFA.

Table 2.2. Summary of measurement techniques used to assess vascular and cerebrovascular function within this thesis.

Measurement Technique	Methodology
Vascular function	
Post-occlusion reactive hyperaemia	Assessment of microvascular function using laser Doppler flowmetry (Stupin et al., 2018, Cracowski et al., 2006).
Flow-mediated dilation	Assessment of macrovascular endothelial function using B-mode vascular ultrasound (Thijssen et al., 2019).
Cerebrovascular function	
CO ₂ reactivity	Assessment of cerebral reactivity to carbon dioxide using transcranial Doppler ultrasound (Koep et al., 2022).
Cerebral autoregulation	Assessment of cerebral autoregulation using transcranial Doppler ultrasound. (Claassen et al., 2016)

2.3. Physical Activity and Exercise

2.3.1. Physical Activity and exercise terminology

Despite being used interchangeably, PA and exercise are terms that have distinct and important differences. These terms are utilised throughout this thesis meaning these distinctions are important to note. PA refers to any bodily movement produced by skeletal muscles that requires energy expenditure (Caspersen et al., 1985). This term includes all movements during leisure time, though it is moderate-to-vigorous intensity PA, specifically, that has been shown to be the specific domain of PA that has the greatest impact on improving parameters of health (Hupin et al., 2015). It should be noted that although the focus of this thesis is largely on MVPA, any increases observed in total PA are also valuable, particularly for the least active individuals given the relationship between PA and health is curvilinear (Powell et al., 2011).

Exercise, on the other hand, is considered a domain of PA that is planned, structured, repetitive and has a final or immediate objective to improve or maintain fitness (Caspersen

et al., 1985). Interventions that target increases in PA and structured exercise levels may improve rates of diseases prevalence and therefore warrant investigation.

2.3.2. The role and importance of physical activity for health

The importance of PA and exercise as a non-pharmacological management strategy in healthcare is irrefutable. Exercise and its role in a healthy lifestyle, has been discussed since ancient civilizations; *“Eating alone will not keep a man well, he must also take exercise”*, as has the importance of maintaining exercise *“that which is used develops, and that which is not used wastes away... If there is a deficiency in food or exercise the body will fall sick”* (Hippocrates, ca 400 BC).

In more recent history, the importance of living a physically active lifestyle was exemplified in the seminal London transport workers’ study (Morris et al., 1953). In this study, bus drivers, who spent a considerable amount of time sitting, were compared to bus conductors, who stand for most of their working day. Morris et al. (1953) observed that drivers had a 42% increased incidence of coronary heart disease compared with conductors, and in drivers it proved more fatal. It was concluded that men in physically active jobs had less coronary heart disease during middle-age and if they did develop disease, it was less severe and developed later than men with physically inactive jobs (Morris et al., 1953). This seminal study not only highlights the necessity of PA but also the issue of prolonged sedentary time (any waking behaviour characterised by a low energy expenditure [≤ 1.5 metabolic equivalents (METs)], while in a sitting, reclining or lying posture), a behaviour that has come to the fore alongside physical inactivity. However, recommendations on completing PA for health did not begin to appear prominently until the 1990’s (Pate et al., 1995). Although these issues are now widely acknowledged, and the range of benefits associated with PA are established and well-known, including primary and

secondary prevention of several chronic diseases (diabetes mellitus, cancer, osteoporosis), and reduced risk of premature death (Warburton et al., 2006) we still face a physical inactivity epidemic. Across the globe, 27.5% of adults do not meet current public health guidelines for PA (Guthold et al., 2018).

The UK PA guidelines state that adults should accumulate at least 150 minutes of moderate intensity activity per week or 75 minutes of vigorous activity; or a combination of both (DHSC, 2019). Previous evidence has shown that not meeting PA guidelines increases the risk of developing several health conditions including obesity, hypertension, type II diabetes mellitus and cardiovascular diseases; all of which lead to a reduction in life quality and expectancy (Lee et al., 2012a). As previously mentioned, physical inactivity is not the only concern; an increasing body of evidence suggests that time spent sedentary may also increase the risk of long-term conditions and mortality (Biswas et al., 2015). Previous research, from Ekelund et al. (2016), explored the ability of PA to offer protection against the negative effects of sedentary behaviour. This highlighted that reducing sedentary behaviour may also offer benefits independent from increasing PA alone, this concept will be discussed further in *section 2.3.4*. Unquestionably, more efforts in the development and implementation of interventions to combat inactivity are warranted. However, given the overwhelming body of evidence for the benefits of PA, the promotion of this available evidence to improve the health of varying populations remains insufficient (Kohl et al., 2012).

2.3.3. Effects of physical inactivity on health

Physical inactivity refers to performing insufficient amounts of moderate to vigorous intensity PA (i.e., not meeting guidelines) (Tremblay et al., 2017). The impact of physical inactivity on international healthcare systems has an enormous burden, conservatively

estimated to total ~\$53.8 billion worldwide (Ding et al., 2016). In fact, inactivity is recognised as the fourth leading cause of death worldwide (Kohl et al., 2012), causing ~5.3 million deaths from non-communicable diseases such as obesity and cardiovascular disease (Lee et al., 2012a). It has been suggested that the importance of PA is often undervalued and underappreciated by those in the public health and clinical medicine sector (Blair, 2009), despite the fact that physical inactivity has been highlighted as a primary target for public health policy (Kohl et al., 2012).

According to the World Health Organization (WHO, 2020), those who are insufficiently physically active have a 20-30% increased risk of all-cause mortality compared to those who meet the guidelines of 150 mins of moderate PA (or equivalent) per week. The lack of progress in the promotion of PA is emphasised by over a quarter of the world's population (1.4 billion people) being not sufficiently active, with no improvement in global levels of PA seen since 2001 (WHO, 2020). There is now an overwhelming body of evidence that highlights the irrefutable benefits of PA but also growing evidence as to the concept of PA as medicine.

A meta epidemiological study including 205 randomised controlled trials ($n = 339,274$ participants) compared the effectiveness of exercise and drug interventions on mortality outcomes to find that exercise had similar effectiveness in reducing mortality outcomes when compared with drug interventions (Naci and Ioannidis, 2013). Further to this we know that PA helps to preserve both physical and mental health and function as we age and reduces the risk of numerous long term conditions (Church and Blair, 2009) – therefore, PA can not only be used as treatment but also as a preventative measure.

2.3.4. The COVID-19 pandemic and physical activity

The global health concern of physical inactivity was accelerated by the COVID-19 pandemic. In March 2020, WHO classified the spread of coronavirus as a global pandemic. As a result, many governments (including the UK) imposed heavy restrictions on day-to-day life for the public. *Social distancing* was brought in to reduce the risk of transmission, with people required to stay at home except for limited purposes such as food shopping, one form of exercise per day (limited to 30 minutes), medical treatment or travelling for work were working from home was not possible. These unprecedented measures undoubtedly influenced PA levels, along with the physical and mental health of whole populations.

A study whereby 3052 US adults self-reported their PA, found that post-COVID restrictions, PA was 32.3% lower in those who had been previously meeting US PA guidelines, with those self-isolating reporting a decrease of ~43% (Meyer et al., 2020). The negative impact of COVID-19 on PA levels was also observed via an electronic survey completed by 1047 people worldwide. It reported that COVID-19 home confinement had a negative impact on all intensity levels of PA, as well as increasing sitting time by 3 hours per day (Ammar et al., 2020). Furthermore, the *Activity and Health during the SARS-CoV2 Pandemic* survey was used by Wilke et al. (2021) to collect data from 13,503 participants across various countries. The results indicated that mean self-reported moderate-to-vigorous physical activity (MVPA) and vigorous physical activity (VPA) were reduced by 41% and 42%, respectively, from pre- to during restrictions. Moreover, 67% of participants reported they were unable to maintain their previous levels of PA. This becomes more striking as pre-restrictions 81% of the participant sample ($n = 10,938$) were compliant with PA recommendations but post-restrictions this had fallen to ~63%, with more than a quarter (28%) of participants previously meeting the guidelines falling short. Reductions in PA such as these can have a negative impact on a variety of health outcomes including both mental health outcomes,

such as increased anxiety (Stubbs et al., 2017) and depression (Schuch et al., 2018), and physical health outcomes, such as reductions in cardiorespiratory fitness, lean body mass and increases in body fat (Bowden Davies et al., 2018). It should be noted that COVID-19 related restrictions lasted over the course of years to differing in severity, meanwhile the aforementioned health consequences have been shown to occur over much shorter periods. These have been shown to occur after as little as 14 days of inactivity (Bowden Davies et al., 2019). Further to this, it has also been shown that reductions in brachial artery diameter and increased markers of vascular cell death have occurred in as little as 3-5 days of inactivity (Boyle et al., 2013). Acute inactivity has also been shown to be detrimental, with only 3-6 hours of uninterrupted sitting being ample to reduce vascular function (Carter et al., 2017, Thosar et al., 2015). Overall, the COVID-19 pandemic accelerated the need for novel, home-based and remote PA interventions. The impact of physical inactivity is clear and was exacerbated by pandemic-related restrictions. Therefore, it is vital that modern PA interventions with a wider reach (e.g., remotely accessible) are researched and developed.

2.3.5. Rheumatoid arthritis and physical activity

2.3.5.1. Historical Perspectives on PA for people living with RA

Although the benefits of PA for people living with RA are now well established and accepted (Cooney et al., 2011); historically, PA has not always been encouraged for people with RA. Until the 1950's PA was, in fact, discouraged amongst people living with RA, with the suggestion that immobility and bed rest would be more beneficial (Pinto et al., 2017). Vigorous dynamic exercises were perceived to be further damaging to joints and understood to upregulate disease activity. Instead, non-weight bearing, isometric, range of motion exercises were preferred as they placed less stress on joints (Jivoff, 1975, Swezey, 1974).

2.3.5.2. Current Perspectives on PA as a management strategy for RA

Over the past ~50years, PA and exercise have been consistently shown to positively impact disease activity and symptoms in people living with RA (Katz et al., 2020), with suggestions that PA may significantly improve both functional ability and quality of life (Katz et al., 2020, Metsios and Kitas, 2018). A review of literature in 2015 (Veldhuijzen van Zanten et al., 2015b) observed that PA and exercise were perceived by patients as making an important contribution to symptom management, in areas such as pain relief (Henchoz et al., 2013), improved joint function (Henchoz et al., 2013) and increased energy levels (Wilcox et al., 2006). This demonstrates a change in attitude towards PA and exercise within the RA community. Interestingly, there was no difference between the perceived benefits of those who exercised and those that did not (Veldhuijzen van Zanten et al., 2015b). However, it also highlights that despite the benefits of exercise for RA being well known, and accepted, people still do not engage with these behaviours (O'Dwyer et al., 2014).

The latest recommendations for PA and exercise in people living with RA closely reflect the aforementioned UK PA guidelines (DHSC, 2019). The overarching principles state that PA is part of a broader management strategy to optimise health related quality of life and has broader health benefits for people living with RA. They also suggest the four domains (cardiorespiratory fitness, muscle strength, flexibility and neuromotor performance) are all applicable and feasible for people living with RA. Moreover, the recommendations also state that PA should be promoted in people living with RA in line with general PA recommendations whilst acknowledging disease specific barriers (Osthoff et al., 2018).

2.3.5.3. The role of PA in managing systemic risk in people living with RA

PA and exercise have not only been shown to improve disease symptoms and quality of life but can also have a positive impact on systemic complications and extra-articular manifestations (UK Chief Medical Officers, 2019, Stavropoulos-Kalinoglou et al., 2013,

Metsios et al., 2013, Metsios et al., 2020). Individualised exercise programmes have been shown to improve vascular function and thereby reduce cardiovascular risk in people living with RA (UK Chief Medical Officers, 2019, Stavropoulos-Kalinoglou et al., 2013, Metsios et al., 2013, Metsios et al., 2020). Furthermore, people with RA who complete regular exercise have shown improvements in aerobic capacity (Van Den Ende et al., 2000), muscle strength (Van Den Ende et al., 2000, Baillet et al., 2011) and mental wellbeing (Kelley and Kelley, 2014) – which all support an improved quality of life and reduced risk of mortality. In a recent narrative review, it was concluded that both aerobic and resistance exercise produce significant beneficial effects on established CVD risk factors, whilst also eliciting positive adaptations in the structure and function of cardiac and vascular systems (Metsios et al., 2020). This is of particular note for the RA community as the biggest cause of mortality for these individuals is CVD (Kitas and Gabriel, 2011). It is therefore of the upmost importance to ascertain why people with RA choose to be active or not and what supports or prevents them from doing so.

2.3.5.4 The COVID-19 pandemic and RA

The COVID-19 pandemic amplified physical inactivity in the general population (Peçanha et al., 2020), and especially so in populations who were classified as high risk (Pérez-Gisbert et al., 2021) including people living with RA (Balchin et al., 2022). This was due to the various advised measures (e.g. shielding) for those who are immunosuppressed (Pinto et al., 2020). Aside from the effects of the pandemic, individuals diagnosed with RA often present with reduced engagement in PA and exercise in comparison to non-RA individuals (Lee et al., 2012b, Summers et al., 2019). Despite the benefits of PA for people with RA being well established (Osthoff et al., 2018), a recent study employing device-based measuring of PA in 129 participants with inflammatory joint disease (>50% with RA) found that only 29% of people were meeting existing PA guidelines (Bell et al., 2022). The lack of

PA undertaken by people with RA has also been shown using accelerometers to measure PA in comparison to the general population, for instance people with RA were less habitually active and more sedentary than healthy, matched controls (Prioreshi et al., 2013). Furthermore, there is further device-based evidence to show that people living with RA complete less moderate-to-vigorous PA (MVPA) than a non-RA control group (Hernandez-Hernandez et al., 2014). With this well observed difference in PA levels in mind, it is pertinent to note a lack of specific reference metabolic equivalent (MET) values for people with RA, as activities such as walking may have a different energy cost (and thus MET and intensity level) due to the effects of the condition (Steultjens et al., 2023). Nonetheless, it is clear that the issue of physical inactivity in RA is irrefutable and should be a focus of future research given the positive impact that upregulating PA affords this clinical group.

2.3.5.5. Barriers and facilitators to physical activity and exercise

2.3.5.5.1. Barriers to PA & exercise for people living with RA

Identifying and understanding barriers and facilitators to PA and exercise is extremely important in order to develop programmes and interventions that promote effective and sustainable PA and exercise for people living with RA. It is important to note that traditional barriers to PA and exercise that are not specifically related to RA will still have a large influence. For example, a review of literature including 22 studies found that 15 cited non-arthritis specific barriers, with eight citing lack of time and four citing the cost exercising as barriers (Veldhuijzen van Zanten et al., 2015b). These studies did included samples with RA patients and other types of arthritis, studies that exclusively contained RA patients found that lack of time was the most consistently reported barrier, followed by lack of motivation (Veldhuijzen van Zanten et al., 2015b). It is vital that these general barriers to PA and

exercise are not ignored, however, RA does present with disease-specific barriers that should be considered in relation to healthcare provision.

The RA specific barriers highlighted in the aforementioned review included reduced mobility/functional ability and stiffness but pain and fatigue, were the most commonly cited. Intriguingly, all of these barriers have been shown to significantly improve once people living with RA commence exercising (Metsios and Kitas, 2018). This presents the relationship between RA, health, PA and exercise as cyclical in nature, with the very symptoms of RA preventing PA that would in turn alleviate those same symptoms. This idea is supported by a study that observed those more physically active RA patients as having a higher self-regulatory efficacy to overcome RA specific barriers (Gyurcsik et al., 2013). Taken together, this suggests that the initial uptake of PA and exercise by people living with RA should be a focus. If it could be possible to overcome these barriers and take the *first steps* to being more active this could ameliorate barriers and lead to more sustained active lifestyles and patient led long-term management.

Symptom specific barriers are not the only condition-specific challenges faced when trying to become more active; qualitative research has demonstrated that lack of provision of RA specific exercise programmes and lack of knowledge of appropriate exercise for people living with RA were also perceived to be barriers to PA and exercise (Veldhuijzen van Zanten et al., 2015b). Furthermore, patients felt that HCPs were also unclear about exercise suitability and programmes for people with RA (Veldhuijzen van Zanten et al., 2015b). If patients are not confident that HCPs are themselves confident in the prescription of exercise and PA, then it is unsurprising that patients lack confidence to take the *first steps* to becoming more active. Particularly, as patients lack of knowledge on appropriate PA and exercise is related to fear of aggravating symptoms and 'damaging' their joints (Veldhuijzen van Zanten et al., 2015b). As a consequence of this, it has been identified that uncertain

and inconsistent advice is provided by consultants regarding exercise for people living with RA (Halls et al., 2017); with HCPs exhibiting only moderate-to-low confidence in prescribing exercise (Law et al., 2013, McKenna et al., 2019). Overall, it appears that relevant training is lacking in HCPs, as well as poor education/awareness in people with RA in terms of becoming more active. To do this, first the literature around exercise interventions in RA must be assessed. This may help to uncover why there is a lack of confidence from HCPs, subsequently allowing for adjustments to improve confidence which may then be transferred to patients.

2.3.5.5.2. Facilitators to PA and exercise for people living with RA

Facilitators to PA and exercise in RA are less researched than barriers. In a review of literature, only 10 studies reported on facilitators (Veldhuijzen van Zanten et al., 2015b) and the most consistent RA specific facilitator was support from healthcare providers. This is interesting given patients experiences of HCPs being unsure on PA and exercise advice. This evidence adds to the notion of the cyclical relationship between RA, health, PA and exercise, whilst also highlighting the vital importance of discovering the source of ill-confidence of healthcare providers to describe PA and exercise in RA. Further to this, it was also reported that social support and experienced/expected positive physical and mental effects were also main facilitators for people with RA (Veldhuijzen van Zanten et al., 2015b).

2.4. Physical Activity and Exercise Interventions

2.4.1. PA and exercise prescription in clinical practice

There is no overarching figure for the number of chronically diseased adults meeting PA guidelines, however it is likely that this number is lower than in non-diseased populations, suggesting the vital importance of PA and exercise prescription within clinical practice. PA is a cornerstone in the primary prevention of at least 35 chronic conditions (Booth et al., 2012), with exercise now also considered a significant first-line treatment for several

chronic disease (Pedersen and Saltin, 2015). As such, exercise is now incorporated in the management strategies of large number of long term conditions, with evidence that in some cases exercise therapy is just as, or more, effective than pharmacological treatments (Pedersen and Saltin, 2006). This is being recognised within UK healthcare, with the National Health Service (NHS) advocating exercise programmes for people with CVD (NHS England, 2019), as well as Public Health England acknowledging the importance of PA in clinical care pathways (Public Health England, 2014). The current approach in people with chronic disease usually involves HCPs advising individuals to begin or increase their PA and/or exercise (Brannan et al., 2019). Individuals can also be referred to exercise referral schemes (ERS) through primary care pathways (e.g. general practitioner [GP]).

2.4.2. Exercise referral schemes

ERS were implemented across the UK in the 1990's, in the absence of any conclusive evidence of effectiveness (Sowden and Raine, 2008). A typical ERS would include a referral from a GP to a leisure centre or gym for supervised and structured exercise, a model that comes from the 2001 National Quality Assurance Framework that is still used today (Department of Health, 2001). Since this framework was published there has also been an Exercise Referral Toolkit (British Heart Foundation National Centre, 2010), which is now outdated, and a PH54: Exercise Referral Schemes guidelines (National Institute for Health Care Excellence, 2014, National Institute for Health Care Excellence, 2018c), that is based on weak evidence. Consequently, ERS are not under any strict regulations that they need to adhere to in terms of programme delivery. There could be advantages to ERS such a broad accessibility and lower costs (~£20,000 per quality-adjusted life year compared to usual care), though often initial patient uptake and adherence to the prescribed exercise is poor (Pavey et al., 2012, Pavey et al., 2011). The loose regulations lead to a diverse array

of ERS, all implementing different principles, a likely reason for differing levels of adherence and subsequent success.

2.4.3. Interventions and exercise prescription to increase physical activity and exercise in rheumatoid arthritis.

As outlined in *section 2.3.6.* there is convincing evidence to suggest that being physically active can help with the management of RA. Research examining the effects of PA and exercise in people living with RA has increased in the 21st century, however, the efficacy of interventions to increase PA and exercise is a lesser investigated area (Conn et al., 2008). As such, over the last decade there has been a lack of progress in terms of promoting and implementing PA and exercise in clinical practice (Metsios and Kitas, 2018). This is concerning as it is clear that promoting PA and exercise in this population is vital for improving health outcomes (Plasqui, 2008, Metsios et al., 2010). Similar to the aforementioned ERS, studies that have endeavoured to make people with RA more active usually suffer from a drop-off in activity afterwards (Metsios and Kitas, 2018). This is unsurprising as, similar to other ERS, there is no detailed guidance on PA and exercise prescription in RA.

People living with RA have been included as part of larger reviews examining the efficacy of interventions to increase PA and exercise. For example, Ezzat et al. (2015) discussed six studies that examined exercise adherence strategies in RA, but only one was rated 'high quality' (Van den Berg et al., 2006) that showed a beneficial intervention effect. The same review also commented on the diversity of interventions employed, with many being multi-faceted, meaning it is difficult to compare results and to determine which component was having a positive effect on exercise adherence in this group. When considering the above it is unsurprising that HCPs do not feel confident in prescribing exercise, despite the fact it is well known to be beneficial. Thus, the lack of guidance and standardisation for PA and

exercise prescription in RA is worrying. To solve this issue and provide better guidance, research interventions aiming to increase PA and exercise in RA must be explored, as well as garnering a greater understanding of the quality of interventions performed previously. The best way to implement an exercise intervention to bring about these positive effects specifically to RA remains elusive.

2.4.4. Issues to address in Exercise Referral Schemes and physical activity interventions.

Despite a lack of guidance as to how to approach implementing exercise and PA into the management of RA, we do already know some issues related to existing ERS and PA interventions in healthcare management. The first factor is the employment of unsupervised exercise interventions. A recent survey examining current delivery approaches within ERS observed higher utilisation of individually completed unsupervised ERS (24) compared with individually completed supervised ERS (20) in England (Rowley et al., 2021). Concerningly, there is an array of evidence from a multitude of clinical and non-clinical populations that suggests unsupervised exercise may be less effective when compared with supervised exercise at improving health outcomes (Umpierre et al., 2011, Lacroix et al., 2017, Fennell et al., 2016, Vemulapalli et al., 2015). There may be many factors that contribute to the diminished effectiveness of unsupervised exercise, but reduced adherence has been cited as a vital factor (Umpierre et al., 2011, Lacroix et al., 2017, Fennell et al., 2016, Vemulapalli et al., 2015). It is known that support and supervision from qualified professionals improves adherence (Morgan et al., 2016a), so it's not surprising that the absence of supervision may elicit a negative effect. Poor compliance has also been observed in unsupervised exercise in comparison to group exercise sessions with social interaction (King et al., 1990). However, there is also evidence to show that minimally supervised home-based exercise programmes can be successful (Kis et al., 2019),

suggesting that there may be a *middle ground* in terms of supervision to ensure successful PA and exercise interventions.

It must be noted that whilst adherence and compliance present an issue in ERS and PA interventions, they are also notoriously poorly reported in research. Adherence has previously been defined as “the extent to which an individual corresponds with the quantity and quality of exercise, as prescribed” (Argent et al., 2018). This suggests that an individual who performs exercise to the required quantity (e.g. number of sessions) might not be classes as adherent if they did not perform the correct quality of exercise (e.g., intensity etc.). This definition may need to be updated as it does not take in to account compliance, which is distinct from adherence. Compliance refers to the conformity to a prescribed exercise plan (e.g., achieving the correct intensity). Therefore, an individual could adhere to an exercise programme should they complete all prescribed sessions, however if sessions were not completed to the correct intensity this would be non-compliant. This approach may not only aid feedback and monitoring but could also aid research reporting and the feasibility of interventions would be clearer.

These issues may be pertinent in upregulating PA and exercise in RA as the latest guidance in RA suggests patients should “*improve general fitness and be encouraged to exercise.*”, only suggesting that hand exercise programmes need to be supervised by a specialist (National Institute for Health Care Excellence, 2018b). Despite unsupervised exercise having advantages such as lower cost and broad accessibility, it is alarming that there is no detailed advice given on implementing supervised exercise and PA into the clinical management of RA. Reduced levels of adherence and compliance that may come about due to lack of supervision is a wide societal issue that may have a large impact on the ability of interventions to change clinical outcomes (Shore et al., 2019). Interestingly, potential reasons for this align with barriers people with RA face to becoming active, such as lack of

knowledge and lack of support and feedback from specialists (Bachmann et al., 2018). Taken together, the evidence around exercise and PA prescription in RA suggests the need to implement novel and effective strategies to overcome current barriers, whilst increasing uptake, adherence, and compliance to prescription.

2.5. Mobile Health Technology

2.5.1. An introduction to mobile health technology

Modern technological advances may hold a solution to improving PA and exercise uptake, adherence, and compliance to personalised exercise prescription. This technology falls under the term; mHealth technology and is defined as *“medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistance, and other wireless devices”* (World Health Organisation, 2017). The use of mHealth technologies has increased in recent times as technology has become more widespread and accessible. The devices used are typically portable, convenient, cost-effective and give the user a sense of control, all of which lends itself for use as an intervention support mechanism (Khaylis et al., 2010, Bacigalupo et al., 2013, Thomas and Bond, 2014). Moreover, fitness and smart watches, from companies such as Fitbit, Apple and Garmin, have become the leading fitness trend in recent years with 19% of Americans owning at least one (STATISTA, 2021). This is further highlighted by a survey from the WHO that found 83% of 112 member countries had at least one mHealth intervention in place (World Health Organisation, 2011).

2.5.2. mHealth for physical activity and exercise prescription

mHealth technology is being utilised more often in PA and exercise interventions, likely due to being practical in any environment, at any time, whilst also being able to collect objective and reliable data (Kooiman et al., 2015, Eapen and Peterson, 2015). Moreover, mHealth technology may also alleviate both internal (e.g., lack of time, lack of motivation) and

external (e.g., travel expense, gym expenses) barriers to PA and exercise due to its remote and accessible nature. Recent research studies have shown that mHealth technology can, effectively promote PA and exercise in a variety of populations including; older adults (King et al., 2016, Larsen et al., 2019), individuals living with musculoskeletal and neurological conditions (Plow and Golding, 2017) and people living with cardiometabolic conditions (Hodkinson et al., 2021).

There are also a very limited number of studies that have assessed the effectiveness of mHealth to promote PA in RA, though not necessarily as a primary outcome measure. Katz et al. (2018) found that use of a *FitBit Zip* pedometer increased PA whether paired with individualised step targets, or not. Similarly, Allam *et al.* (2015) found that gamification via a web based intervention increased PA in RA whether paired with online social support or not. Another internet-based PA intervention with individual tailored supervision, exercise equipment and group contacts for people with RA proved more effective in encouraging patients to meet PA activity guidelines than an internet-based program without additional elements (Van den Berg et al., 2006). Taken together this shows the potential for success in using mHealth technology to upregulate PA and exercise in RA, though additional elements may need to be considered when providing mHealth led PA interventions in RA. As such, it has been recommended that technology-based interventions should include the following five components: self-monitoring, counsellor feedback and communication, social support, structure and principals of behaviour changes and individual tailoring (Khaylis et al., 2010).

Combining mHealth technology with additional components seems vital to achieve meaningful PA behaviour change. For example, Brickwood *et al.* (2019) suggested that interventions which integrated a multifaceted approach were more successful in increasing PA participation compared with controls. Similar evidence has been reported for the

effectiveness of a multifaceted mHealth approach in adults with cardiometabolic disorders (Hodkinson et al., 2021). The limited research within RA has shown a comparable example, with the addition of social support to a web-based intervention having no significant difference (Allam et al., 2015). Conversely, Van den Berg *et al.* (2006) found that additional components such as exercise equipment, tailored supervision and group contacts enhanced the intervention effects on PA. It should be noted that the heterogeneity in PA monitoring and reporting results in difficulty drawing conclusions from comparing between studies. Despite this, there are still clear potential benefits for the use of mHealth technology when trying to prescribe and increase PA and exercise. The promising potential of mHealth to impact PA behaviour change is somewhat dulled by the suggestion that the rapid growth of mHealth technology has outpaced the capacity of HCPs to employ it in a patient-centred manner to yield a meaningful change (Feldman et al., 2018). However, it could also be argued that if HCPs have less time capacity, mHealth technology could help to remove the barrier of time constraints leading to more efficient PA and exercise prescription.

2.5.3. mHealth for clinical use

It has been suggested that new technologies such as mHealth possess the capacity to enhance the value and availability of healthcare (Bashshur et al., 2014). As many as 2.5 billion people worldwide own a mobile phone, providing huge potential for mHealth to facilitate better access to clinical diagnostics and advice (Rowland et al., 2020). Further to this, according to a recent survey in the US, 56% of physicians have discussed mHealth with patients, and 26% have been asked by patients about mHealth (Rowland et al., 2020). Currently, the NICE and the NHS categorise mHealth apps according to their functionalities, with mHealth technologies for PA and exercise likely falling under tier 3a: for preventing and managing disease, used alongside treatment and likely to have measurable user

benefits, encompassing preventative behaviour change and self-management (National Institute for Health Care Excellence, 2018a)

Apps and wearable technologies (e.g., fitness watches) are most likely to be used within this area, acting as platforms to support the delivery of behaviour change interventions. It has been suggested that they can improve engagement with existing and well-established behaviour change strategies through mechanisms like personalised goal setting and gamification (Perski et al., 2017). This is conveyed in the literature, with most studies involving mHealth to improve PA incorporating behaviour change techniques observed as successful (Mateo et al., 2015, Brickwood et al., 2019). However, whilst the challenge of achieving sustained improvements that elicit clinically meaningful change remains, long-term follow-up data is limited (Brickwood et al., 2019). The mHealth technology interventions detailed within this thesis were informed by social cognitive theory (SCT), which proposes that the interaction between people (personal), their behaviour, and their environment can affect human behaviour (Bandura, 1986). This was deemed a relevant theory as the use of mHealth technology to support an intervention to increase PA requires interception between personal, environmental and behavioural factors.

Moreover, the quality of mHealth research is highly variable with few of the applications tested readily available on app stores [Android and iOS] (Singh et al., 2016). As well as this, many mHealth developers do not have access to funds for large trials, and may be under pressure to demonstrate shorter-term growth with retrospective analysis of already marketed apps instead of more rigorous, but lengthy, RCT's (Rowland et al., 2020). Clinicians may struggle to interpret and utilise data from such research, leading to a lack of application (Rowland et al., 2020). In addition, due to the rapid advancement of mHealth technology both healthcare system regulatory structures and professional education and training programmes lag. Therefore, it is vital that HCPs are supported in their competency

with mHealth related matters (Moss et al., 2019) so the information being relayed to patients is correct. To achieve this, thorough research must be conducted to assess whether mHealth technology can be utilised to create a clinically meaningful change.

**CHAPTER 3: ADHERENCE TO UNSUPERVISED
EXERCISE IN SEDENTARY INDIVIDUALS: A
RANDOMISED FEASIBILITY TRIAL OF TWO
MOBILE HEALTH INTERVENTIONS
(MOTIVATE LJMU)**

3.1. Introduction

There is overwhelming evidence that regular PA and exercise are vital for prevention and management of long-term conditions (Pedersen and Saltin, 2015). Nevertheless, worldwide 27.5% of adults do not meet the global recommendations of 150 minutes of moderate, or 75 minutes of vigorous-intensity PA per week (Guthold et al., 2018). A contributing factor could be ineffective public health strategies, including those within primary healthcare settings, which recommend or employ unsupervised exercise in inactive healthy individuals and those with long-term conditions (Umpierre et al., 2011, Vemulapalli et al., 2015, Lacroix et al., 2017, Fennell et al., 2016).

Unsupervised exercise has the advantages of low cost and broad accessibility, especially at a population level and when targeted at those with long-term conditions by healthcare professionals. However, there is evidence from meta-analyses that suggest unsupervised exercise may be less effective compared to supervised training at improving health outcomes in a variety of long-term conditions (Umpierre et al., 2011, Vemulapalli et al., 2015, Lacroix et al., 2017, Fennell et al., 2016). Although several factors may contribute to the ineffectiveness of unsupervised exercise, poor adherence has been cited as an important consideration (Umpierre et al., 2011, Vemulapalli et al., 2015, Lacroix et al., 2017, Fennell et al., 2016). Poor adherence (adherence referring specifically to performing the recommended number of exercise sessions) is evident in healthcare settings, such as ERS research studies (Morgan, 2005, Pavey et al., 2012), some of which include the addition of behavioural counselling that is thought to enhance adherence (Roy et al., 2018, Hesketh et al., 2021a). Poor adherence and compliance (compliance referring specifically to achieving the recommended duration and intensity of exercise sessions) to prescribed exercise is a huge societal problem that impacts on the ability of an intervention to

positively change clinical outcomes (Shore et al., 2019, Palazzo et al., 2016). Potential reasons for poor adherence and compliance to unsupervised exercise centre around lack of knowledge, lack of personalisation and lack of support/feedback from exercise specialists (Morgan et al., 2016a, Bachmann et al., 2018). Therefore, effective strategies to overcome these barriers and increase adherence to unsupervised exercise are required.

One potential solution is to explore how technology could be used to enhance personalised exercise prescription and thus improve adherence and compliance to unsupervised exercise. Such technologies, including mobile health (mHealth) wearables, could be used to (i) provide virtual guidance during exercise (e.g., the use of fitness videos); (ii) allow remote exercise support from health professionals that allows communication and feedback (e.g., personalised text messages); (iii) provide instant, individual biometric feedback during exercise (e.g., exercise intensity via heart rate). The primary aim of this study was to, therefore, investigate the feasibility of two mHealth technology supported exercise interventions to increase adherence to unsupervised exercise.

Given that the exercise interventions in the current study are unsupervised and home-based/remote, the study also aimed to investigate the feasibility of employing remote measurement techniques. Whereby participants collect health outcomes from home, known as a 'remote clinical trial'. Previous research studies employing unsupervised exercise interventions report high participant drop-out (Roy et al., 2018, Jung et al., 2020a, Hesketh et al., 2021a) and missing data for key physiological or clinical outcomes. This may be explained by availability, time, and travel distance for research facility visits. Remote physiological data collection may therefore enhance participant retention and minimise data loss in time-intensive studies such as exercise interventions.

The specific objectives were to:

1. Determine the feasibility of a home-based exercise and PA counselling intervention, supported by mHealth biometrics.
2. Determine the feasibility of a home-based exercise intervention supported by the provision of virtual exercise resources.
3. Determine the feasibility and fidelity of measurement techniques to assess adherence to unsupervised home-based exercise interventions.
4. Determine the feasibility of collecting basic health outcomes using remote measurement techniques.

3.2. Methods

3.2.1. Study design

A feasibility, parallel group randomised trial was adopted using 1:1 randomisation, whereby participants completed baseline assessments prior to completing a 12-week intervention. Interventions delivered were either home-based exercise supported by online resources (online resources) or mHealth supported exercise and PA counselling (MOTIVATE), following which measurements were repeated (Figure 1). The reporting of this study conforms with the CONSORT 2010 statement: extension for pilot and feasibility trials (Eldridge et al., 2016) (Supplementary File 1) and TIDieR guidelines for reporting of interventions (Hoffmann et al., 2014) (Supplementary File 2). The study was approved by Liverpool John Moores University ethics committee (20/SPS/031) and adhered to the *Declaration of Helsinki*. The protocol was prospectively registered on clinicaltrials.gov (identifier: NCT04979702).

3.2.2. Participants and setting

Participant recruitment took place between August 2020 and July 2021. Recruitment occurred via emails sent to businesses in the North-West of England and advertisements on social media. Inclusion criteria required that participants were insufficiently active adults (not currently meeting UK PA guidelines(UK Chief Medical Officers, 2019)), aged between 18-75 years, with no known cardiovascular or metabolic disorders, who were able to exercise safely as deemed by completion of The Physical Activity Readiness Questionnaire (PARQ+; 2020 version). Participants were guided through the PARQ+ by a member of the research team. Exclusion criteria were pregnancy or planning to become pregnant in the next 3 months, <6 months postpartum or breastfeeding <1 month before recruitment and not owning a smartphone with a data plan or access to Wi-Fi. Participant screening took place via telephone or video call (Zoom Video Communications Inc., 2016). Written informed consent was obtained using the eSignature solution HELLOSIGN, in line with Health Research Authority (HRA) advice (Sept 2018).

3.2.3. Randomisation and blinding

Participants were randomly allocated using a computer-generated sequence to either the MOTIVATE or online resources groups by an independent researcher. Participants were notified of their group via email prior to baseline testing. By design, the researcher and participants were aware of the group allocation.

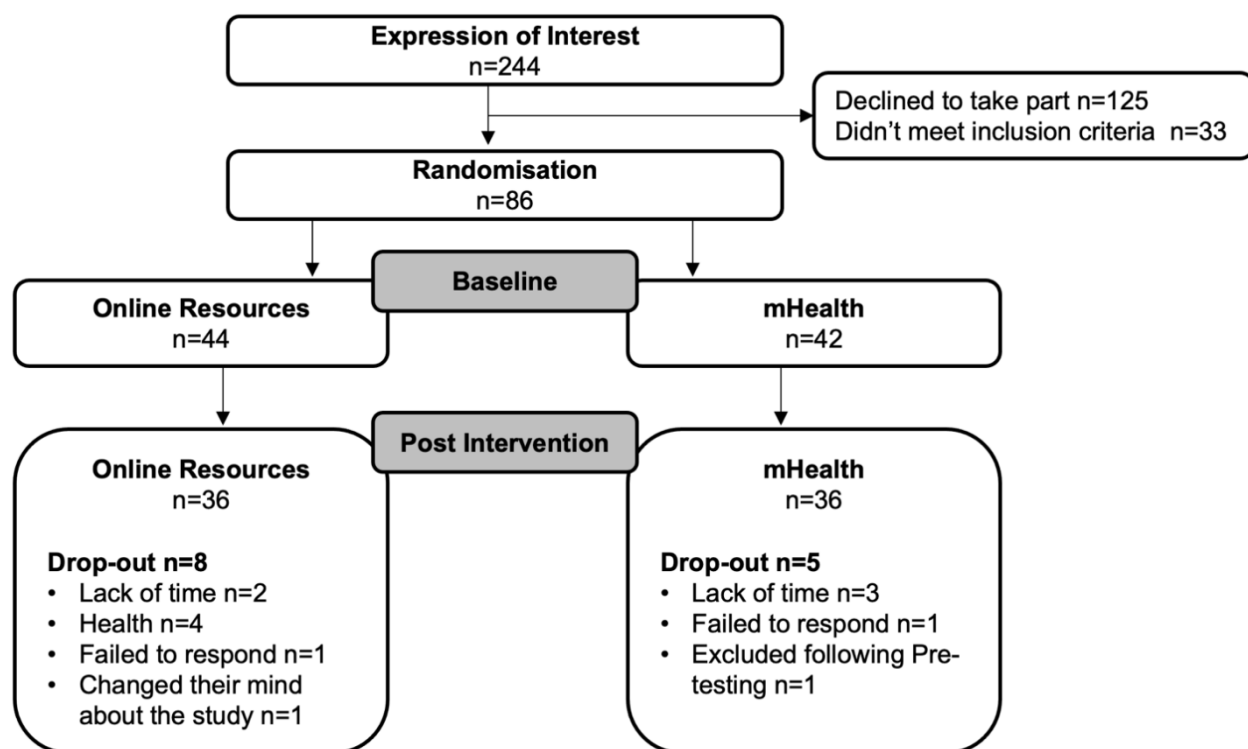


Figure 3.1. Participant consort diagram.

3.2.4. Interventions

All participants undertook a 12-week intervention. Participants could combine exercise training modes to suit individual preference but were encouraged to complete 3 exercise sessions per week. This frequency is in line with the exercise guidelines for people with Type 2 Diabetes, which recommends exercise on at least 3 days/week with no more than 2 consecutive days without exercising (Mendes et al., 2016). In addition, several studies employing supervised exercise have shown such a frequency to be effective for improving health outcomes (Maxwell et al., 2021, Hesketh et al., 2021a, Scott et al., 2018).

Online Resources: Participants were given access to a website that provided virtual resources and instructions to assist in performing a progressive exercise programme for the 12-week duration. Exercise prescriptions for four different exercise types were available to each participant on the website; moderate-intensity continuous training

(MICT), vigorous-intensity training (VIT), high-intensity interval training (HIIT) and resistance training (RT) (details of the exercise prescriptions are outlined in Supplementary Tables 1-4). The website included weekly overviews (in written and video format) of the prescribed sessions for each exercise type, with instructions on total session duration, duration of phases (e.g., warm-up and work and rest periods) and intensity using rate of perceived exertion (RPE, CR-10 scale (Borg, 1998)). Instructional videos with demonstrations were available for individual HIIT and RT sessions.

mHealth supported exercise with PA counselling (MOTIVATE): The mHealth intervention is based on a recently developed intervention entitled MOTIVATE (Hesketh et al., 2021c). Participants received a series of exercise counselling sessions supported through mHealth technology that consisted of an online coaching platform, a smart phone app and a wrist worn fitness watch. Participants also had access to the website and virtual resources outlined for the online resource group. Participants co-developed a personalised and progressive exercise programme with an exercise specialist (exercise specialists had an undergraduate degree in sport and exercise science along with specific training in exercise prescription, supervision and motivational interviewing) generally based on the four exercise types outlined above; MICT, VIT, HIIT and RT. Nevertheless, participants could include other activities such as exercise classes, dance or sport depending on personal preference. As part of their exercise counselling sessions, participants were also encouraged to increase their daily habitual PA (PA outside structured planned exercise sessions(American College of Sports Medicine, 2014)) by enhancing awareness of the guidelines/recommendations, drawing participants attention to the activity target on their smartwatch (see below) and discussing tips for increasing PA. Built into the 12-week program was behavioural exercise counselling. Participants had 4 virtual counselling

sessions (Zoom Video Communications Inc) with their exercise specialist (Supplementary Table 5). The content of these meetings was based upon the primary prevention specific consultation guide developed by the “Moving Medicine” initiative (https://movingmedicine.ac.uk/consultation-guides/condition/adult/primary-prevention/more_minute/) and the Brief Action Planning guide and flow chart developed by The Centre for Collaboration Motivation and Innovation (<https://centrecmi.ca/brief-actionplanning/#1502747767988-85883f98-7299>).

mHealth technology: The exercise prescription was delivered, and progression monitored by 3 synchronised mHealth elements;

1. Online platform for exercise specialist (Polar Flow for Coach, www.polar.com/coach): The exercise specialist programmed the agreed co-developed exercise intervention, specifying the agreed number of sessions per week and the type of exercise. The exercise specialist inputted the individual exercise sessions, prescribing the duration and intensity (measured through HR) of each phase within the session i.e., warm up, workout and cool-down. These detailed exercise sessions were then available as pre-set sessions on the participant’s fitness watch. Throughout the intervention the online platform also provided the exercise specialist with access to the participants training and PA data including daily PA, HR traces from each exercise session, RPE (CR-10 scale ratings (Borg, 1998)) following exercise sessions and individual written comments on exercise sessions provided by the participants.
2. Smart phone app for participant (Polar Flow – Sync & Analyze): Participants used the app to access their exercise programme and to track exercise and PA achievements. All data recorded by the fitness watch was available within the app

and participants were able to provide feedback on each exercise session including a session RPE (Borg, 1998) and written comments on each exercise session.

3. Fitness watch (Polar Ignite, Polar Electro, Finland): Participants were given a Polar Ignite fitness watch, which featured a triaxial accelerometer and optical HR monitor. Progress towards a personalised PA target was displayed throughout the day on the watch screen. Participants were able to access pre-set exercise sessions, designed by their exercise specialist, on the device. The prescribed duration and intensity, via HR zones, was displayed in real time on the watch throughout the exercise session. The watch also provided live visual and haptic (vibration) alerts, coaching participants to execute the session as prescribed (i.e., HR zone and duration). If participants did not want to use pre-set exercise sessions the monitor screen still provided live visual feedback on exercise time and intensity (current HR).

On-going virtual communication with Exercise Specialist: During the first 4 weeks participants were asked to provide RPE and written comments following all exercise sessions, using the app. The comments related to the appropriateness of the session's duration and intensity and their enjoyment of the session and exercise type. After each recorded exercise session, the exercise specialist used the feedback to send a personalised text message in response to the session. Based on this feedback, the exercise specialist updated the training programme and pre-set exercise sessions as appropriate (changing exercise duration, intensity, rate of progression or type), using the online platform. The aim of this initial period was to refine the exercise sessions to ensure participants had a programme that fit with their current fitness, lifestyle, and exercise goals. Following exercise counselling 3 (at 4 weeks), participants received weekly text messages from their exercise specialist. The exercise specialist continued to use the data recorded in the online

platform to provide personalised messages, but participants did not have to leave feedback after each exercise session during this period.

The design of the MOTIVATE programme was informed by social cognitive theory (Bandura, 1986). The intervention components were focussed on Michie and colleagues' taxonomy of behaviour change technique (Michie et al., 2011) categories, including "Goals and Planning," and "Feedback and Monitoring" and motivational interviewing technique processes, including "Engaging" and "Evoking" designed to promote long-term adherence to PA and exercise. These mechanisms were considered appropriate to improve competence to exercise and PA engagement, and autonomous motivation for exercise and PA to enhance uptake and maintenance of exercise and PA.

3.2.5. Outcome measures

3.2.5.1 *Intervention feasibility*

Intervention adherence and compliance: Three methods were used to assess intervention adherence and compliance as a measure of feasibility.

1. *Device derived measurement of exercise sessions:* Optical HR monitoring was used to record HR during exercise sessions. The online resources group were provided with a Polar OH1 for the duration of the trial and asked to wear it during structured exercise sessions. However, the monitor was not paired with a smart watch or phone, meaning HR data was stored but no real-time /historic feedback was available to participants. As such, the online resources group remained blinded to HR throughout the intervention. For consistency of measurement with the online resources group, data for the MOTIVATE group was collected using a Polar OH1 optical HR monitor paired to the Ignite fitness watch provided as part of the

intervention. Using the data uploaded to www.flow.polar.com the following metrics of adherence and compliance were assessed (Hesketh et al., 2021a):

- Training drop-off: defined as the week during which participants no longer completed any training sessions.
- Programme Adherence: defined as the % of prescribed sessions completed, where 100% adherence was 36 sessions (3 sessions/wk for 12-wks).
- Compliance: was defined differently for each exercise type (MICT, VIT, HIIT, RT), see Supplementary Table 9 for detailed information, but generally refers to the achievement of both a prescribed duration and intensity. Compliance is presented as intention-to-treat and per protocol. Intention-to-treat analysis used all consented participants, and it was assumed that missing HR data represented a missed training session. Per protocol analysis, included only data from completed training sessions.

2. *Survey-reported exercise behaviour:* Information about participants' quantity, frequency, and intensity of exercise participation was assessed using the Godin Leisure Time Exercise Questionnaire (GLTEQ) (Godin and Shephard, 1997). The GLTEQ was administered at baseline, post-intervention and 4, 6 and 8 weeks into the intervention, via an online form (www.googleforms.co.uk). To assess adherence and compliance to the prescribed programmes the number of sessions of moderate and strenuous intensity exercise of at least 30 minutes in duration was calculated. This outcome closely reflected the expected prescription during the final week of the intervention.

3. *Device derived physical activity:* A subset of participants ($n=75$; online resources $n=38$; MOTIVATE $n=37$) wore a wrist-worn tri-axial accelerometer (GT9X, ActiGraph, Pensacola, FL, USA), over a 7-day period at baseline and post-intervention. A recording window of 7 days, starting at midnight on the day of baseline and post-intervention assessments was utilised. The accelerometer was pre-set to record at 30Hz to account for transit in the post, while optimising the battery life of the device. Accelerometer data was downloaded using ActiLife version 6.11.9 (ActiGraph, Pensacola, FL, USA) and analysed using the open-source R software package, GGIR (R package for accelerometry) beta v1.6-1 (<https://cran.r-project.org/web/packages/GGIR/index.html>). GGIR performs autocalibration with the reference of local gravity (Van Hees et al., 2014b). Raw acceleration data were used to compute Euclidean norm minus one (ENMO in mg)(Van Hees et al., 2013a). Data were analysed from the first to the final midnight using 5-second epochs. Participants were included in the main analysis if they achieved a minimum of 10 hours of wear time for a minimum of 4 days, including at least 1 weekend day. Non-wear was detected if the standard deviation (SD) of two axes was < 13 mg with a range of < 50 mg in windows of 60 minutes. Time spent in activity intensities was established using published thresholds (Hildebrand et al., 2014, Hildebrand et al., 2017). Sedentary time was defined as time accumulated below 45 mg, light PA was defined as ≥ 46 mg and < 100 mg, moderate PA was defined as ≥ 101 mg and < 428 mg, and vigorous PA was defined as ≥ 429 mg. The following metrics of PA were assessed, MVPA recorded in ≥ 10 -minute bouts (MVPA10+), number of weekly minutes of total, light, moderate, vigorous and MVPA and number of weekly minutes of sedentary time.

Qualitative evaluation of intervention feasibility: Semi-structured interviews conducted at post-intervention aimed to understand experiences (barriers, facilitators, actual use of technology and exercise specialist, receptivity to the exercise specialist, perceived appropriateness, and suggestions for improvement) with the interventions (technological aspects and exercise prescription and counselling). Two participants from mHealth ($n=1$ male) and 4 participants from online resources ($n=2$ males) volunteered for post-intervention interviews. All interviews were conducted via telephone or video call (Zoom Video Communications Inc), according to participant preference, and were structured using a topic guide (Supplementary Tables 6-8).

At post-intervention, all participants were invited to complete an anonymous online survey. The survey was specific to the intervention completed (Supplementary Table 10-11). Questions were developed, piloted within, and revised by the research team using appropriate literature (Scott et al., 2019).

3.2.5.2. Feasibility of monitoring unsupervised home-based exercise

Device derived measurement of exercise sessions: Participants in the online resources group were asked what proportion of exercise sessions they wore the OH1 HR monitor for (0%, 0-33%, 33-66% and 66-100%).

Survey-reported exercise behaviour: The number of moderate and strenuous intensity exercise sessions was assessed by the GLTEQ post-intervention and compared with the number of exercise sessions recorded by the OH1 HR monitor during the final week of training. Comparisons were performed for all participants, MOTIVATE only, online resources only, and online resources who reported a wear proportion of 66-100%.

Device derived physical activity: Availability of data using 10h and 16h wear-time criteria (minimum of 4 days, including at least 1 weekend day) was assessed.

The ability of the accelerometer to detect exercise sessions was assessed. A subgroup of participants was asked to wear the accelerometer and fitness watch concurrently at week 12 of the intervention. Using the timestamp from PolarFlow, HR and ENMO data were aligned to allow comparison of the proportion of exercise sessions spent in moderate-to-vigorous intensity activity. Comparisons were performed for MICT, VIT, HIIT and RT sessions. Thresholds used for moderate-to-vigorous activity were $\geq 101\text{mg}$ (Hildebrand et al., 2014) and $\geq 60\%$ HR_{max} for accelerometer and HR measures, respectively.

Qualitative evaluation of monitoring unsupervised home-based exercise: Semi-structured interviews were conducted at two time points, 1) following baseline and 2) following post-intervention assessments. Five participants ($n=3$ males) volunteered for baseline interviews, whilst 2 participants from mHealth ($n=1$ males) and 4 participants from online resources ($n=2$ males) volunteered for post-intervention interviews. Semi-structured interviews at baseline and post-intervention aimed to learn about experiences (ease and willingness, and suggestions for improvement) with all three monitoring approaches.

3.2.5.3. Feasibility of remote measurement techniques

Prior to baseline assessment, participants were mailed, via parcel force, all the necessary assessment resources. Items requiring immediate return (accelerometer) were mailed by participants, via Royal Mail to the appropriate destination using pre-paid envelopes, but all other resources were kept by the participant. Prior to post-intervention testing participants

were mailed, via Royal Mail, an accelerometer. Written guidelines explaining the assessments were sent alongside testing resources, and videos were available on the study website. Participants received a call from a member of the research team before baseline testing to outline measures and answer any questions. Calls were not routinely provided prior to post-intervention testing. Researchers were remotely available on the day of testing if required. All assessments were completed following an overnight fast, having abstained from caffeine, alcohol, and vigorous exercise for 24h. Data (participant characteristics, anthropometrics and BP) was sent to the research team using an online reporting form (www.googleforms.co.uk).

Participant characteristics: Participant completed an online form (www.googleforms.co.uk) to provide basic demographics. This included collection of participant home postcodes which was used to report Index of multiple deprivation (IMD)(Ministry of Housing Communities & Local Government, 2015). This index estimates a deprivation score and is categorised into quintiles based on income, employment, education, health, crime, housing, and environment information.

Anthropometrics: Participants were sent a tape measure (Seca 201, Germany) and electronic scales (Salter, UK). Participants were asked to record their height if known, if not, participants used the tape measure to record height. Waist circumference was measured in triplicate at the level of the umbilicus. Previous work suggests a strong correlation between self-measured and technician-measured height, body mass (Kushi et al., 1988) and waist circumference, measured at the umbilicus (Brown et al., 2018).

Blood pressure: Participants were sent an automated BP monitor, validated by the British and Irish Hypertension Society (UK, Salter BPA-9200-GB; CA, Bios BD215) and measured BP in triplicate following 10 min seated rest. Self-measured BP is a validated approach for monitoring BP, endorsed by the American Heart Association and American Medical Association (Shimbo et al., 2020b).

SF-12 Questionnaire: Participants completed an online version (www.googleforms.co.uk) of the SF-12 Health Survey.

Qualitative evaluation of remote measurement techniques: Semi-structured interviews at baseline and-post intervention ($n=9$) aimed to learn about experiences (ease and willingness, comprehension, and ability to follow instructions, length of time to complete, suggestions for improvement) with remote testing.

Following baseline measures all participants were invited to complete an anonymous online survey. The survey asked participants about their demographics, experiences of the data collection process and the measures taken (Supplementary Table 12).

3.2.5.4. Sample Size

The target sample size that was deemed feasible for this trial was 80 participants (40 per group). Such a sample size is higher than the median value for pilot studies (36 participants per arm) reported in an audit of pilot and feasibility trials registered in the UK clinical research network (Billingham et al., 2013). Sample sizes between 24- and 50 have been recommended for feasibility trials (Sim and Lewis, 2012). Our sample size is larger than both of these recommendations.

3.2.5.5. Analytical methods

The potential impact of the interventions on continuous outcomes was reported as mean $\pm$ SD and estimates of effect (95 % confidence interval) within interventions (baseline to post-intervention). Cohen's d effect sizes (Cohen, 1998) were reported and interpreted as: small <0.4 , moderate $0.4-0.8$, and large >0.8 .

Spearman's rho coefficient was calculated to determine the association and the bivariate correlation coefficient between GLTEQ and HR monitor derived, and accelerometer and HR monitor derived outcomes. The (r) value was interpreted as 0.0 to 0.2 very weak to negligible correlation, 0.2 to 0.4 weak to low correlation, 0.4 to 0.7 moderate correlation, 0.7 to 0.9 strong, high correlation and 0.9 to 1.0 very strong correlation (Landis and Koch, 1977). In addition, Bland-Altman analyses determined the level of agreement between GLTEQ and HR monitor derived, and accelerometer and HR monitor derived outcomes (Bland and Altman, 1986). Plots with mean difference and limits of agreement (± 1.96 SD) and levels of agreement were assessed between the measures.

Data obtained via semi-structured interviews were audio recorded and transcribed verbatim. Interview transcripts were thematically analysed manually via a six-phase process (Braun and Clarke, 2006, Braun and Clarke, 2012): data familiarisation, generating codes, searching for themes, reviewing themes (narrowing in relation to feasibility of; remote testing, an mHealth exercise intervention and monitoring unsupervised exercise), defining and naming themes and writing up. Themes were produced based on patterns of response and relevance to the pre-determined categories formed by the research questions. Flexibility in analysis was driven by both the prevalence (number of interviewees

articulating the theme) and the importance given to the information. This method of coding allows all interview information to be thematic with focal points for discussion and future recommendations acknowledged (Clarke et al., 2015). Primary analysis was conducted by AC with frequent debriefing sessions with the research team to discuss, challenge and reframe the thematic structure.

The qualitative survey responses from open questions were analysed using a framework approach (Ritchie and Spencer, 2002), which has been used previously within mixed method studies (Scott et al., 2019).

3.3. Results

Between August 1, 2020, and July 31, 2021, $n=244$ people expressed an interest in the study, of these $n=209$ were eligible and $n=86$ participants were recruited (Figure 1). Participants were randomised to online resources ($n=44$, females $n=29$) or MOTIVATE ($n=42$, females $n=28$) groups. Baseline characteristics are presented in Table 1.

Table 3.1. Baseline participant characteristics (mean $\pm$ SD).

	MOTIVATE ($n=42$)	Online Resources ($n=44$)
Age (years)	45 $\pm$ 11	47 $\pm$ 11
Weight (kg)	81.9 $\pm$ 19.4	81.6 $\pm$ 17.0
Height (cm)	168.7 $\pm$ 7.6	167.0 $\pm$ 16.0
BMI (kg/m ²)	29 $\pm$ 6	31 $\pm$ 16
Waist circumference (cm)	95 $\pm$ 19	97 $\pm$ 14
SBP (mmHg)	115 $\pm$ 15	117 $\pm$ 16
DBP (mmHg)	79 $\pm$ 8	80 $\pm$ 11
MAP (mmHg)	96 $\pm$ 14	98 $\pm$ 13

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MA: mean arterial pressure; IMD: index of multiple deprivation.

3.3.1. Intervention feasibility

Intervention adherence and compliance: Adherence and compliance to prescribed exercise, measured via optical HR monitor (Table 2), indicates participants in MOTIVATE group exercised more regularly than prescribed. No exercise uptake (completed 0 training sessions) was 5% in MOTIVATE ($n=2$), and 39% ($n=17$) in online resources. During the final week of the intervention 79% ($n=33$) of MOTIVATE participants were completing prescribed exercise sessions compared with 14% ($n=6$) in online resources. Supplementary Figure 1 displays the percentage of participants still completing training sessions at each week of the intervention.

Table 3.2. Adherence and compliance assessed by device derived measurement of exercise sessions.

Outcome	MOTIVATE ($n=42$)	Online resources ($n=44$)
Number of sessions per week (n)	3.4±2.0	0.7±1.0
Total adherence (% of 36) [n]	113±68 [$n=41±24$]	22±34 [$n=8±12$]
Compliance (% of 36 sessions completed correctly)	83±43	14±27
Per protocol compliance (% of recorded sessions completed correctly)	73±24	36±41

Intention-to-treat data displayed, except for per-protocol analysis for compliance which included only recorded sessions.

The effect size was large for the change in survey reported exercise behaviour (number of sessions of moderate and strenuous intensity exercise obtained from the GLTEQ) from baseline to post-intervention for participants in MOTIVATE (baseline 0.9±1.1, post-

intervention 3.9 ± 3.1 ; $d = 0.88$, $CI = 0.49$ to 1.26) and moderate in online resources (baseline 1.1 ± 1.7 , post-intervention 3.1 ± 2.9 ; $d = 0.63$, $CI = 0.27$ to 0.99).

The effect size was moderate for an increase in MVPA10+ for participants in MOTIVATE (58 ± 125 min $d = 0.47$, $CI = -0.06$ to 0.98 , Table 3). The effect size for a decrease in sedentary time was also moderate for participants in the MOTIVATE group (68 ± 139 min $d = 0.49$, $CI = -1.0$ to 0.04 , Table 3).

Table 3.3. Baseline and post-intervention scores for remotely measured outcomes.

Outcome	MOTIVATE					Online resources				
	<i>n</i>	Baseline	Post-intervention	95% CI for baseline to post score difference	Effect Size	<i>n</i>	Baseline	Post-intervention	95% CI for baseline to post score difference	Effect Size
Anthropometrics										
Weight (kg)	35	81	83	-0.22, 0.45	0.11	35	81	80	-0.74, 0.05	-0.40
BMI (kg.m ²)	35	28	29	-0.22, 0.45	0.12	35	28	28	-0.72, -0.03	-0.38
Waist circumference (cm)	35	91	89	-0.60, 0.08	-0.26	35	94	89	-0.73, 0.05	-0.39
Blood Pressure										
SBP (mmHg)	34	114	115	-0.25, 0.42	0.09	35	117	117	-0.32, 0.34	0.01
DBP (mmHg)	35	78	79	-0.30, 0.37	0.04	35	79	79	-0.42, 0.24	-0.09
MAP (mmHg)	35	94	96	-0.13, 0.54	0.21	35	98	98	-0.36, 0.30	-0.03
SF-12										

Physical (PCS-12)	32	50	52	-0.13, 0.58	0.23	33	52	51	-0.37, 0.32	-0.03
Mental (MCS-12)	32	42	48	0.07, 0.79	0.43	33	43	47	-0.03, 0.67	0.32
Physical Activity										
MVPA10+	16	81	139	-0.06, 0.98	0.47	21	123	137	-0.32, 0.54	0.12
MVPA	16	472	475	-0.48, 0.50	0.01	21	536	479	-0.69, 0.18	-0.26
Total PA	16	1427	1364	-0.61, 0.37	-0.12	21	1612	1330	-0.81, 0.08	-0.37
Light PA	16	969	897	-0.66, 0.33	-0.17	21	1085	869	-0.76, 0.12	-0.33
Moderate PA	16	459	454	-0.51, 0.47	-0.02	21	518	455	-0.73, 0.14	-0.30
Vigorous PA	16	13	20	-0.26, 0.73	0.24	21	18	24	-0.25, 0.61	0.18
Sedentary time	16	8563	8086	-1.01, 0.04	-0.49	21	8331	8202	-0.52, 0.34	-0.09

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SF-12: 12-Item Short Form Survey; PCS: physical health component score; MCS: mental health component score; PA: physical activity; MVPA: moderate-to-vigorous PA; MVPA10+: MVPA recorded in ≥ 10 -minute bouts.

Qualitative evaluation of intervention feasibility: Themes that arose from analysis of participants' interviews are represented in this section using verbatim quotes to depict the participants' perspective. Three key themes were developed during analysis. These themes included variety and flexibility of the programmes, support mechanisms, and barriers to exercise adherence.

Theme 1: Variety and flexibility of the programmes: Participants in both groups enjoyed the variety of exercise types on offer and the ability to adapt and progress the programme as it was ongoing. However, MOTIVATE participants discussed the importance of their exercise specialist in refining the programme.

"... if it was do the same exercises throughout, I think I would have struggled to do the full twelve weeks three, four times a week of HIIT, or it would have felt like a chore." (MLJMU 06, online resources)

"I liked the different...varieties of exercise..." (MLJMU103, online resources)

"I really liked that it had so many different options available to it...I liked that the programme was adaptable, and over time working with [exercise specialist], I was able to tweak it to what I was liking..." (MLJMU52, MOTIVATE).

Theme 2: Support mechanisms: Participants in both groups reported that they felt well supported during the programmes. Online resources participants cited the importance of the resources available, and that the website was clear, easy to follow and provided good support to complete the programme:

"I found the instructions really clear and the website really useful, and so I intended to use that to guide me each week, so I'd click on one week at a time to see what I should be doing, and initially I found it motivated me to exercise more and get out."

(MLJMU103, online resources)

MOTIVATE participants discussed the importance of the relationship built between themselves and the exercise specialist as well as the importance of the text message feedback in this process:

"So, you kind of develop a bit of a relationship with someone (exercise specialist) who can then work with you. (Exercise specialist) can make suggestions about things that I don't know about, and it did feel very important, yes." (MLJMU 73, MOTIVATE)

"...they (text messages) were little jogging memories of what I'd done, and just like little support as well to keep up the good work... the personal angle of it was nice..."

(MLJMU59, MOTIVATE).

The importance of the support provided through the participant app and fitness watch were also discussed by MOTIVATE participants. Participants particularly liked how the technology allowed them to keep track of their PA and exercise levels and adapt the programme schedule around their lifestyle. The importance of using HR to guide exercise sessions and the greater understanding of exercise intensity through this were also discussed.

"I loved seeing the graphs on the (participant app), so I could see which days, like there was essentially a pattern as to what my activity levels were like a week... the

graph kind of gave you evidence about what you have been doing.” (MLJMU59, MOTIVATE)

”...I really like it. I want to keep it... it gives me information about me that I wouldn’t otherwise have, so what my heart rate’s doing, and it helps me keep track of an exercise” (MLJMU 52, MOTIVATE)

However, both groups discussed how the support received could have been improved. MOTIVATE participants cited adding a community aspect to the programme would have been valuable but highlighted that this could have been difficult due to covid restrictions. MOTIVATE participants also suggested the drop in feedback level (i.e., text messages) across the programme was too drastic and could have been reduced to a lesser extent. Finally, the availability of quick guides for how to use the technology were discussed.

“...that community aspect, because I remember finding it really useful having a chat with other participants, and I realise at the moment anything in real life is tricky, but whether there would be a regular opportunity in other times for a monthly meet-up or something so people could actually meet each other and see how they’re doing, I think would be really valuable” (MLJMU52, MOTIVATE).

“...or at least not drop it (text messages) quite as low as just one text a week” (MLJMU52, MOTIVATE).

Online resources participants suggested that the addition of a diary to track their exercise achievements would have been useful alongside prompts to encourage adherence with programmes.

"Maybe doing some kind of exercise diary might have helped, you know." (MLJMU 02, online resources)

"...maybe a reminder to go and check, like an automatic email to go and check the website more or just a reminder, "Have you done your training session today?"
(MLJMU 02, online resources)

Theme 3: Barriers to exercise adherence: Interestingly the barriers to completing exercise were similar between groups with the external barriers weather, injury and lack of time all discussed, although the adaptability of the home-based interventions was mentioned as a strength here, with participants able to modify sessions when required.

"When it was bad weather, I would use the bottom step of our stairs and get a good audio book, and so do it that way instead" (MLJMU52, MOTIVATE).

"...there's a time issue there that's been more of a struggle..." (MLJMU02, online resources).

"In fact I actually did more exercise than I probably would have done normally, to the point where I then over-exercised and injured myself, so I had to kind of rein it back in a bit..." (MLJMU 103, online resources)

Online survey: Sixty-nine (MOTIVATE $n=33$, online resources $n=36$) participants completed the online survey following the intervention. Based on the survey responses, two key themes, and further sub-themes were developed: 1) the COVID-19 pandemic and 2) Motivation, with the sub-themes, (i) accountability, (ii) communication and feedback, (iii)

tracking, (iv) flexibility of the intervention, and (v) environmental. Supplementary Table 13 shows the frequency of participants positive and negative responses relating to each theme.

3.3.2. Feasibility of monitoring unsupervised home-based exercise

Device derived measurement of exercise sessions: 36 (82%) participants in the online resources group answered the question what proportion of exercise sessions they wore the OH1 HR monitor. 17 (47%) participants wore the monitor for 66-100% of sessions, 2 (6%) wore the monitor 33-66% of sessions, 15 (42%) wore the monitor 1-33% of sessions and 2 (6%) did not wear the monitor for any sessions.

Survey-reported exercise behaviour: 100% of participants, excluding dropouts, completed the GLTEQ questionnaire at baseline ($n=86$) and post-intervention ($n=72$). GLTEQs were completed by 73 (100%), 71 (99%) and 65 (90%) participants at 4, 6 and 8 weeks, respectively.

The correlation coefficients comparing the number of moderate and strenuous intensity exercise sessions assessed by the GLTEQ and HR monitor were 'very weak to negligible/weak' when all participants ($r = 0.20$), MOTIVATE ($r = -0.13$) and online resources ($r = 0.35$) and online resources participants reporting a wear proportion of 66-100% ($r = 0.23$) were assessed. Bland-Altman analyses highlighted a mean difference of 2.1 ± 3.1 sessions, 1.5 ± 3.3 sessions, 2.8 ± 2.8 sessions and 3.6 ± 3.3 sessions for all participants, MOTIVATE only, online resources only and online resources participants reporting a wear proportion of 66-100%, respectively. The limits of agreement for all groups were wide and

suggest the presence of a measurement bias for all groups, as the majority of points fall above the zero line (Figure 2).

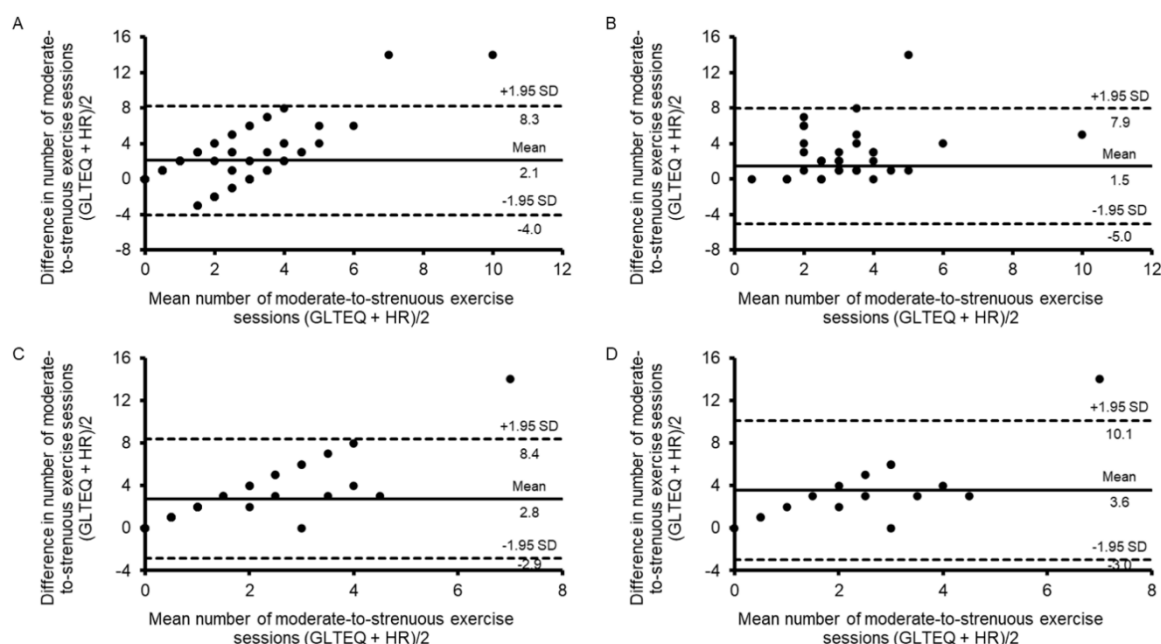


Figure 3.2. Bland–Altman plots assessing agreement for the number of moderate-to-strenuous exercise sessions recorded by the GLTEQ survey and HR monitor. (a) All participants, (b) MOTIVATE only, (c) online resources only and (d) online resources participants reporting a wear proportion of 66–100%. Solid line shows the mean difference in the number of sessions, and the dashed lines show 95% CI of agreement.

Device derived physical activity: Accelerometers were sent to 75 participants (MOTIVATE 37; online resources 38) at baseline and post intervention. Accelerometers were returned by 74 (99%) participants at baseline and 72 participants post-intervention (96%). From returned monitors ≥ 10 h wear time (≥ 4 days, including at least 1 weekend day) was achieved by 67 (91%) participants at baseline and 37 (73%) participants post-intervention. When 16h wear time was used as the criterion, valid wear time dropped to 40 (54%) participants at baseline and 20 (39%) participants post-intervention.

HR monitor and accelerometer traces were available for 11, 7, 12 and 7 MICT, VIT, HIIT and RT sessions, respectively. Two sessions (1 VIT, 1 HIIT) involved exercise on a cycle ergometer and were excluded from the analysis. Representative accelerometer and HR

monitor traces recorded throughout bouts of MICT, VIT, HIIT and RT are shown in Figure 3. Correlation coefficients of the proportion of exercise sessions spent in moderate-to-vigorous intensity activity between the accelerometer and HR monitor were weak, and negative for MICT ($r=-0.16$), VIT ($r=-0.15$) and HIIT ($r=-0.58$) and very weak to negligible for RT ($r=0.14$). Bland-Altman analyses show a mean difference of $-22.6\pm40.5\%$, $-28.8\pm38.6\%$, $-57.0\pm31.2\%$ and $-39.8\pm26.4\%$ for MICT, VIT, HIIT and RT, respectively. Limits of agreement for all exercise types were wide and suggest the presence of measurement bias during all exercise types, as the majority of points fall below the zero line (Figure 4). None of the HIIT or RT sessions met the criteria for MVPA10+. Accelerometer and HR monitor traces recorded throughout bouts of VIT and HIIT conducted on a cycle ergometer are shown in Supplementary Figure 2 (these were the only sessions conducted on a cycle ergometer).

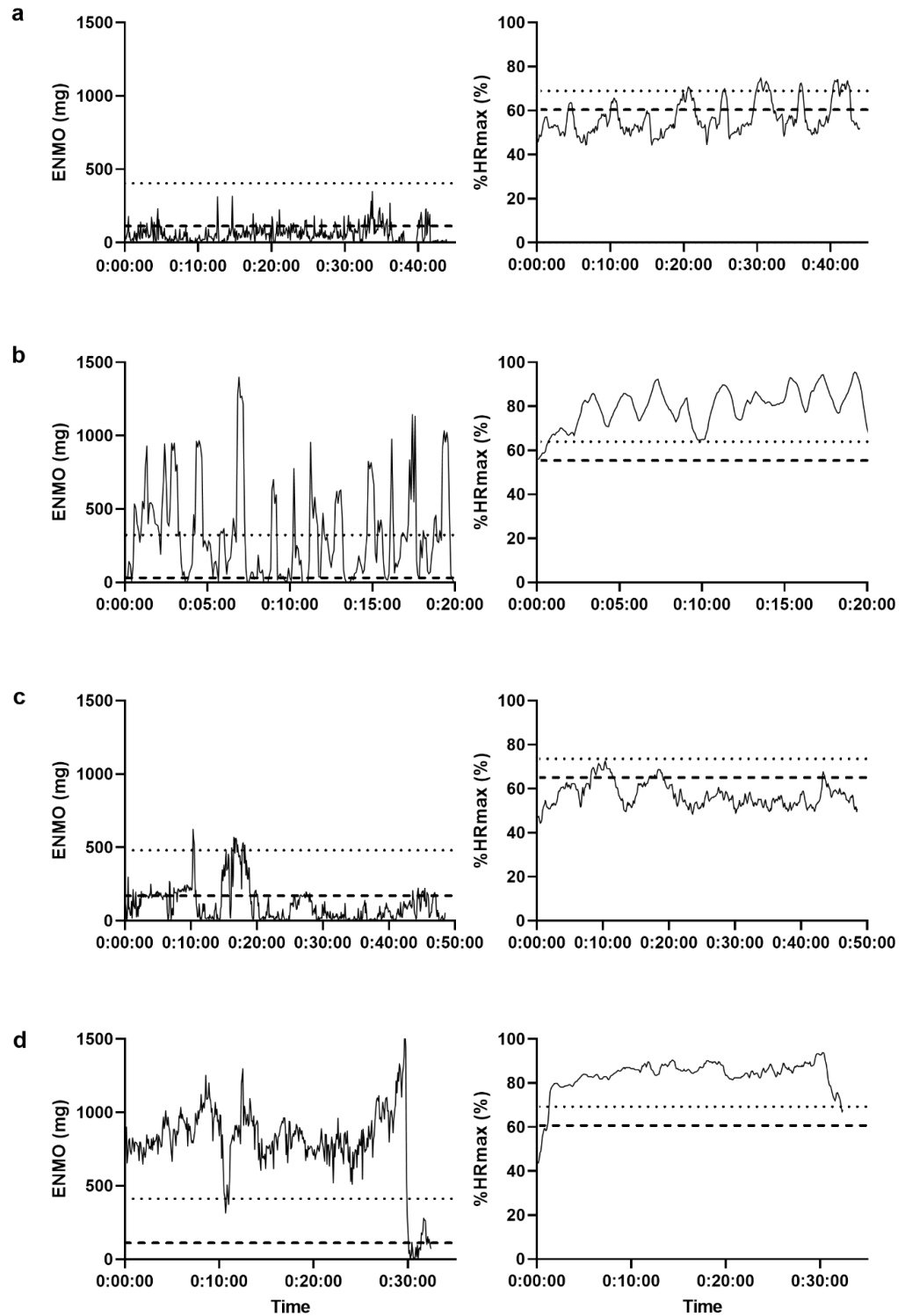


Figure 3.3. Representative accelerometer (mg) and HR data (%HRmax) traces recorded throughout bouts of RT (a), HIIT (b), MICT (c) and VIT (d). The dotted line is indicative of the vigorous intensity threshold (>429 mg/70%HRmax), the dashed line is indicative of the moderate intensity threshold (>101 mg/60%HRmax). (Jung et al., 2020b)

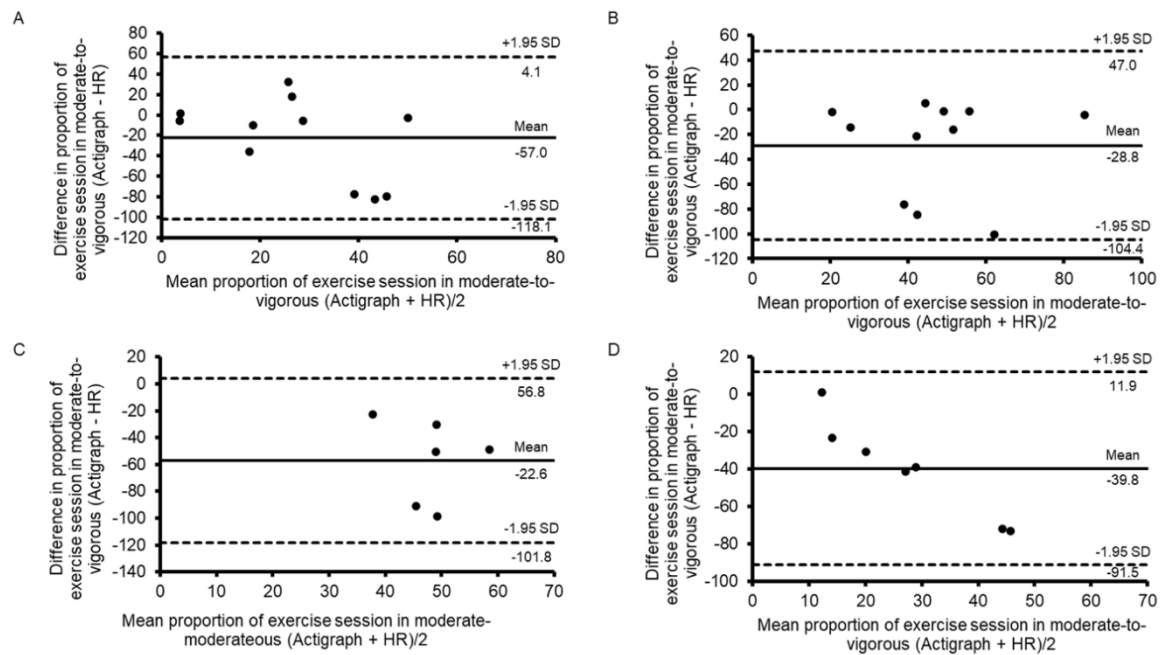


Figure 3.4. Bland–Altman plots assessing agreement for proportion of exercise session in moderate-to-vigorous-intensity activity recorded by the accelerometer and HR monitor. (a) MICT, (b) VIT, (c) HIIT and (d) RT. Solid line shows the mean difference in % time spent in moderate-to-vigorous-intensity activity, and the dashed lines show 95% CI of agreement.

Qualitative evaluation of monitoring unsupervised home-based exercise: In general participants found the ActiGraph accelerometer acceptable to wear for seven days: “I forget it’s there, to be honest with you...I thought was going to be a much bigger thing than it was...” (MLJMU75, MOTIVATE).

Participants in the online resources group struggled with use of the OH1 HR monitor. Participants reported that it was not very user-friendly and that they often forgot to wear it.

“...it would have been more useful to have an activity monitor that was also a heart rate monitor that I just wore for the entirety of the study, because I think there was definitely sometimes where I’d go for a run and realise halfway round that I’d left the heart rate monitor at home, but I had the activity monitor on” (MLJMU25, online resources)

3.3.3. Feasibility of remote measurement techniques

Data availability: Participant flow through the study and reasons for drop-out are shown in Figure 1. Of the 86 consented participants 72 (MOTIVATE $n=36$; online resources $n=36$) completed post-intervention testing, which represented an overall drop-out rate of 16% (MOTIVATE 14%; online resources 18%). When dropouts were considered, 90% of data was available. Though with dropouts removed, data availability was 97%. Reasons for missing data are shown in Table 4. Participants lived a range of 1-284 miles drive (4-303 min) from the university (32 ± 60 miles; 47 ± 63 min). The mean IMD quintile were 3 ± 1 .

Table 3.4. Proportion of available data with reasons for remotely measured outcomes at baseline and post-intervention.

Outcome	Participants <i>n</i>	Baseline		Participants <i>n</i>	Post-intervention	
		% data available (<i>n</i>)	Reason for missing data (<i>n</i>)		% data available (<i>n</i>)	Reason for missing data (<i>n</i>)
Anthropometrics	86	100 (86)	N/A	72	97 (70)	Did not want to take (2)
Blood Pressure	86	100 (86)	N/A	72	97 (70)	Did not want to take (2)
SF-12	86	98 (84)	Did not fill out (1)	72	92 (66)	Did not fill out (2)
			Completed incorrectly (1)			Completed incorrectly (4)

Anthropometrics include height, weight, BMI, and waist circumference.

Preliminary effectiveness: The effect size was moderate for the decrease in body mass ($d = -0.42$, CI = 0.76, 0.07) in online resources and MOTIVATE groups, respectively (Table 3). There was also a moderate effect sized improvement in the mental health component of the SF-12 health questionnaire in the MOTIVATE group ($d = 0.43$, CI 0.07, 0.79).

Qualitative evaluation of remote measurement techniques: Four key themes were developed during analysis. These themes included resources given to support testing, understanding of measurements, completing measurements at home and logistics of posting equipment.

Theme 1: Resources given to support testing: Participants reported that the resources given to help complete the testing (i.e., testing booklet, videos, checklists) were very clear and easy to use and that the visual aspect of the resources were particularly helpful:

“Really good and really clear. I liked the visual aspect, looking at the booklet, the photos were there, all really clear. I didn’t need to use the videos, but I did look at one of them, just as an additional resource, and again, it was step by step. I knew exactly what I had to do, when I had to do it and how it had to be done... They kind of went hand in hand (booklet & checklist), and yes, they were fab” (MLJMU75, MOTIVATE).

Participants also reported that the pre-testing call with a member of the research team was helpful to being able to complete the testing: “...a Zoom call, I thought that was the best resource...I was able to ask the question...just to get total confirmation that I was doing things right” (MLJMU10, online resources).

Theme 2: Understanding of measurements: Participants also reported that they had a good understanding of the measurements, nothing came as a surprise as it was clear what was being measured and why: *“I wasn’t surprised by anything that was on the list or even where we were discussing what would be involved. I think it was all quite what you’d expect”* (MLJMU75, MOTIVATE).

Theme 3: Completing measurements at home: Participants found completing the majority of measurements at home, independently, relatively easy and non-time consuming. They reported that everything was explained well in the pre-testing meeting, and they did not feel the need to have the researcher present as a result: *“because everything was explained so well beforehand, I was quite happy just doing it myself... No, no problems...”* (MLJMU10, online resources group).

Theme 4: Logistics of posting equipment: In general, the logistics of posting testing equipment to participants worked well, participants reported receiving their packages in a timely manner: *“They said they were going to send it out on the Thursday, and I received it on the Friday, so it was super-quick”* (MLJMU75, MOTVATE group) and *“I think it came earlier than they’d actually said, and then everything was in there...”* (MLJMU08, online resources).

Online survey: 78 (MOTIVATE $n=39$, online resources $n=39$) participants completed the online survey following baseline measurements. Outcomes from the closed questions are presented in Supplementary Table 14.

3.4. Discussion

The primary aim was to investigate the feasibility of two mHealth technology supported exercise interventions to increase adherence to unsupervised exercise. The direction and magnitude of the effect sizes suggest that both interventions could be used to invoke potentially meaningful increases in exercise behaviour. Nevertheless, the largest effects were evident following the MOTIVATE intervention, including survey-reported exercise behaviour, time spent in purposeful MVPA (MVPA10+) and adherence to the intervention. The present study also demonstrates that using a combination of methods (i.e., HR monitoring, accelerometry and surveys) may be an essential approach in measuring adherence. Additionally, remote data collection that incorporates self-testing as part of an exercise intervention is feasible. Appropriately powered randomised control trials are now required to explore the effectiveness of the MOTIVATE intervention on enhancing exercise adherence in primary and secondary care.

3.4.1. Intervention feasibility

MOTIVATE: Exercise interventions for insufficiently active individuals, who are recommended unsupervised exercise, need to promote high adherence to impact non-communicable disease. Adherence of $113\pm68\%$ in MOTIVATE, based on sessions captured via the optical HR monitor, demonstrating participants exercised more than the recommended 3 times per week. Furthermore, compliance in performing the exercise sessions to the correct intensity was $73\pm24\%$, and 79% of participants were still exercising during the final week of the intervention. Findings from our laboratory have previously reported adherence levels to exercise of 30-47% in a UK ERS using a similar exercise intervention design to the online resources group in the current study with additional HR

monitoring (Hesketh et al., 2021a). Taylor et al. (1998) reported 45% attendance rate (via gym sign-in) to a gym-based UK ERS. Moreover, Jung et al. (2020a) reported that participants exercised 2-4 times per week (self-reported) following a brief exercise counselling intervention. Ultimately, the current study provides preliminary evidence that MOTIVATE mediates higher adherence to unsupervised exercise than in previous interventions in insufficiently active individuals. Furthermore, there was evidence of a moderate increase in time spent in purposeful MVPA (MVPA10+; 58 ± 125 min/week), which suggests an increase in incidental PA of ~ 1 hour, and a moderate decrease in SB (68 ± 139 min/week) following MOTIVATE. These changes are broadly in line with previous meta-analyses using technology in self-monitoring interventions (Baskerville et al., 2017, Compennolle et al., 2019). Thus, findings demonstrate that MOTIVATE is helpful in mediating positive changes in structured exercise and habitual PA behaviour.

The post-intervention interviews and survey highlighted participant perceptions of the MOTIVATE intervention. Participants considered the flexibility of the intervention and variety of exercise types as instrumental in facilitating session adherence, which is supported by previous research (Morgan et al., 2016b). Unsurprisingly, support from the exercise specialist was also important in facilitating adherence. Particularly, participants found the refining of the programme and regular text messages from the exercise specialist significant facilitators. To the authors knowledge, this is the first intervention to use mHealth technology and biometrics to support this two-way connection. It can be hypothesised that this relationship enhanced participant confidence to perform and manage free-living exercise, which has been deemed essential when initiating new behaviours (Bandura, 1997, Jung et al., 2020a). Finally, participants highlighted the importance of mHealth technology in facilitating adherence to the intervention,

specifically, the role of HR feedback during exercise and the overall PA goal. Previous work has suggested that the availability of live HR data facilitates training programmes by educating participants on how to exercise at an intensity most likely to elicit health changes (Miller et al., 2014) and by developing autonomous motivation through feelings of competence (Kinnafick et al., 2018). Given the positive participant perceptions, the current data suggests that MOTIVATE is feasible for implementation within an insufficiently active population.

Online resources: Based on sessions captured via the optical HR monitor, participants in the online resources group show exercise adherence levels of $22\pm34\%$, with 14% of participants training during the final week of the intervention. This is lower than MOTIVATE and previous trials using similar intervention design with technology to measure adherence (Hesketh et al., 2021a). However, the post-intervention online survey indicated that many participants did not use the HR monitor to record sessions, suggesting this data likely underrepresents adherence to the online resources intervention. Although the GLTEQ may not reflect adherence to the prescribed exercise programme, the change in the number of sessions of moderate and strenuous intensity exercise increased with a moderate effect size (increase from 0 to 1 exercise session per week). The online resources intervention also had negligible effects on PA and SB. Given the limitations of the accelerometer in detecting MVPA during exercise, this is not surprising, as unlike MOTIVATE, the online resources programme did not have a daily PA target. Participants considered the flexibility and variety of the intervention as important and the resources available on the website as instrumental in facilitating adherence. Taken together, the current study provides evidence on some positive changes in exercise behaviour. Nevertheless, future research studies, that choose to employ the online resources intervention, should consider including behaviour

change techniques targeting habitual PA, incorporating self-monitoring and social support based on participant feedback.

3.4.2. Feasibility and fidelity of monitoring unsupervised home-based exercise

Monitoring unsupervised home-based exercise presents unique challenges that must be overcome. Data on the dose of exercise and PA is essential to evaluate the efficacy of any intervention (Shore et al., 2019). To the authors knowledge, this is the first study to evaluate the feasibility and fidelity of techniques to measure adherence and compliance to unsupervised exercise programmes. It is important to establish what outcomes each of these measures provide and whether they are sound indicators of adherence. Firstly, optical HR monitoring was used to provide information on the number of planned structured exercise sessions completed and the intensity of those sessions. HR monitoring has previously been advocated as accurate in assessing exercise responses, providing objective personalised data, that accounts for age, body mass and fitness level (Nes et al., 2017). The approach was feasible in MOTIVATE, where participants wore the monitor as part of the intervention and provided rich data. However, the approach was less feasible in the online resources group, where participants used a blinded monitor only for structured exercise, with less than 50% of participants wearing the monitor regularly. Secondly, the GLTEQ was used as a low burden measure of quantity, frequency, and intensity of exercise participation (Godin and Shephard, 1997), with the expectation that the survey would closely reflect adherence to the exercise prescription during the final week of the intervention. The survey provided excellent data availability throughout the intervention period (≥ 90 of data available at all time points). However, the correlation statistics demonstrated poor validity for measuring adherence when compared to the optical HR monitor, and the Bland-Altman analyses indicated inherent measurement error

(as suggested by the wide confidence intervals) and the presence of measurement bias. Finally, a wrist-worn accelerometer was used to assess PA. Accelerometer derived MVPA10+ has been used as the primary outcome measure in PA and exercise interventions where increasing ambulatory activity has been the primary goal (Taylor et al., 2021). However, previous reports have cited potential issues when using accelerometers to assess non-ambulatory activity, promoted during the current interventions (Matthew, 2005). To the authors knowledge, this is the first study to compare HR and accelerometer defined time in MVPA during structured exercise. The correlation statistics and Bland-Altman analysis demonstrated poor validity for RT and HIIT, both performed through body weight exercises, likely due to the large static component of these complex movements (Matthew, 2005). However, the correlation statistics and Bland-Altman analysis were also poor for ambulatory MICT and VT. This finding was unexpected and warrants exploration with larger data sets. Therefore, the following preliminary statements and recommendations for monitoring adherence to unsupervised exercise and PA interventions based on the feasibility data: (i) employ a combination of methods to assess adherence; (ii) device derived HR provides rich data and should be employed but ways to increase wear time for blinded HR monitors is required, (iii) daily PA is important given the potential for compensatory reductions throughout the day (Paravidino et al., 2021) but accelerometers provide a poor measure of adherence to prescribed exercise and should not be used as standalone measurement, (iv) the GLTEQ survey did not reflect adherence to prescribed exercise and future research may look at ways of improving validity given the low cost, low burden nature of this tool.

3.4.3. Feasibility of remote measurement techniques

Previous research investigating unsupervised exercise interventions report high amounts of missing data, primarily due to high participant drop-out, which jeopardises validity (Roy et al., 2018, Jung et al., 2020a, Hesketh et al., 2021a). The current study employed a remote clinical trial design with the aim of improving participant retention to outcome measurements. To the authors knowledge this is the first exercise and PA trial to assess the feasibility of such an approach. Importantly, overall participant drop-out was lower (16%) than trials employing traditional laboratory testing (24% to 49%) (Roy et al., 2018, Jung et al., 2020a, Hesketh et al., 2021a). A concern with the use of remote clinical trials has been poor protocol adherence, leading to a high proportion of missing data (McDermott and Newman, 2021). However, availability of data for anthropometrics, BP, and the SF-12 questionnaire was high (baseline $\geq 98\%$; post-intervention $\geq 92\%$). Participant experiences of remote testing also appeared to be positive with interviews highlighting the importance of clear testing resources and support in the process. Overall data availability was good, suggesting that future repeated measures studies should consider employing remote clinical trial designs with appropriate strategies to reduce participant drop-out.

Health inequalities plague research findings due to non-diverse recruitment of participants, specifically those from low socioeconomic status' households (Noonan and Simmons, 2021, Font et al., 2011). Previous research proposes that a range of variables, other than just occupational income, influence health inequalities (Font et al., 2011). Furthermore, studies in rural residents suggest that health disparities could be partially due to a lack of access to, knowledge about, and participation in clinical trials (Young et al., 2015, Unger et al., 2018). Participants in the current study lived on average 36 (SD: 75) miles drive away from the university. In addition, the observed spread of deprivation scores in both groups (3 ± 1

AU) highlights the reach of the study design to enhance participation of those typically underrepresented in research. Nevertheless, the current study's recruitment strategies targeted Merseyside employees. Despite this limited targeting, a wide spread of degree and extent of deprivation exists in Merseyside (Eames et al., 1993). Therefore, data is likely representative of the UK population. These preliminary findings highlight the ability to increase access to and inclusivity in clinical trials in those from a range of socioeconomic backgrounds using remote methods.

As expected in the current study's insufficiently active but healthy cohort, changes in health outcomes were negligible. However, data shows that a remote clinical trial design for an exercise and PA intervention was feasible and included measures that would be essential in clinical populations. A common measure usually included within exercise and PA intervention studies is cardiorespiratory fitness (CRF). CRF is a strong predictor of all-cause mortality (Lee et al., 2010) and can be improved with exercise. The gold standard measure of CRF is VO_{2max} and is traditionally measured using breath-by-breath oxygen uptake during incremental exercise to exhaustion on a treadmill or cycle ergometer, which is unlikely to be feasible remotely. There are a number of techniques that aim to provide estimates of CRF, with non-exercise prediction models (Jackson et al., 1990), step tests (Bennett et al., 2016) and mHealth technologies (Klepin et al., 2019, Carrier et al., 2020) showing evidence of accuracy to predict VO_{2max} . Although these approaches show promise and ideally should be included in future remote clinical trials, further research is needed to validate their reliability to track changes in CRF and their feasibility for remote testing.

3.4.4. Limitations and methodological considerations

The decision for two active trial arms rather than a no-treatment control group was informed by the research question, which aimed to inform the design of future unsupervised exercise and PA interventions (RCTs). This strategy allowed us to examine the feasibility of two intervention strategies that differed significantly in their approach, with high levels of participant support versus minimal participant support, thereby adding to the translational value of these data. The authors acknowledge the lack of a follow-up period, and this should be included in the design of future RCTs.

3.4.5. Conclusion

The current study suggests that both interventions, online resources and MOTIVATE, have a positive impact on exercise behaviour. Yet, greater improvements in adherence and PA were observed within the MOTIVATE intervention arm. Nevertheless, to maximise adherence to unsupervised exercise, future appropriately powered trials should explore the effectiveness of the MOTIVATE intervention in insufficiently active individuals and those with chronic disease. Finally, findings demonstrate the feasibility of remote measurement techniques for data collection in exercise and PA intervention trials.

**CHAPTER 4: PROMOTING PHYSICAL
ACTIVITY USING MOBILE HEALTH
TECHNOLOGY IN PEOPLE LIVING WITH
RHEUMATOID ARTHRITIS: MOTIVATE RA**

4.1. Introduction

RA is a chronic inflammatory autoimmune disease characterised by synovial and systemic inflammation, tenderness, swelling and pain in the joints, physical incapacity and the presence of several co-morbidities (Gibofsky, 2012). RA affects approximately 1% of the worldwide population (Symmons et al., 2002), with females two to three times more likely to be affected than males (Scott et al., 2022). As well as symptoms of pain and stiffness reducing the capacity to function normally day to day (Chang et al., 2009), people living with RA display decreased health-related quality of life in comparison to the general population (Wells, 2009).

Individuals diagnosed with RA often present with reduced engagement in PA and exercise, relative to their non-RA counterparts (Lee et al., 2012b, Summers et al., 2019). This has been demonstrated previously through the use of accelerometers to objectively measure PA. For example, it has been observed that people living with RA were less habitually active and more sedentary than matched controls without RA (Prioreshi et al., 2013). Likewise, people living with RA have been observed to spend less time completing MVPA than a non-RA control cohort (Hernandez-Hernandez et al., 2014). Further support comes from self-reported data; a study completed across 21 countries, using multiple questionnaires (e.g., Health Assessment Questionnaire), found that 60-80% of people with RA were physically inactive, with no regular exercise (Sokka et al., 2008). The study also identified that physical inactivity was associated with higher disease activity (i.e., DAS 28 score), as well as symptoms including pain and fatigue (Sokka et al., 2008). Further to this, it has been demonstrated that those living with RA who are more active, scored higher in every aspect of the Short Form-36 questionnaire (quality of life) compared to their less active counterparts (Prioreshi et al., 2013). This highlights the positive impact that regular PA may have on overall health, quality of life and disease symptoms in people living with RA.

The wide range of benefits associated with PA are now well established, however until as late as the 1950's PA was strongly discouraged for people living with RA; instead, bed rest and immobility were favoured (Pinto et al., 2017). This approach has since been dispelled as modern research has shown beneficial effects of increased PA in people with RA, whilst not adversely affecting disease activity (Cooney et al., 2011). In fact, disease activity and symptoms have been shown to consistently benefit from PA and exercise (Katz et al., 2020) suggesting that PA may improve disease activity and severity by improving both functional ability and quality of life (Metsios and Kitas, 2018). A review reported that aerobic exercise improved functionality, quality of life and pain in people with RA, but did not improve disease activity (Baillet et al., 2010). However, a more recent review has shown disease activity (DAS28) was reduced in people with RA, though not to statistical significance, as well as improving functionality (Hernández-Hernández and Díaz-González, 2017). Furthermore, a two-year high intensity exercise programme combining both aerobic and resistance exercise resulted in significant improvements in functional ability of people with RA compared with non-exercise controls (de Jong et al., 2003). Walking is utilised within this study as it represents a low cost activity and requires little training, whilst having been shown to be feasible, acceptable and safe activity for people living with rheumatoid arthritis (Baxter et al., 2016b)

Despite these benefits and a change in perception of PA and exercise in RA, many people with RA remain inactive. Compounding this, physical inactivity in people living with RA was amplified during the varying restrictions of the COVID-19 pandemic as the COVID-19 restrictions (e.g., social distancing and isolation/shielding measures) were found to have increased physical inactivity among RA patients (Pinto et al., 2020). Whilst there is an abundance of research on the effects of exercise and PA on RA, there is very limited research on how to upregulate and promote PA within the population (Cramp et al., 2013,

Larkin et al., 2015). This is concerning as existing evidence clearly demonstrates that exercise and PA have a positive effect on RA and could constitute complimentary therapy, yet still generally people living with RA remain inactive (Lee et al., 2012b, Summers et al., 2019).

Currently, public health strategies, including those within primary healthcare settings, recommend or employ unsupervised exercise in active healthy individuals and those living with long term conditions (Umpierre et al., 2011, Vemulapalli et al., 2015, Lacroix et al., 2017, Fennell et al., 2016). Whilst unsupervised exercise has the advantages of low cost and broad accessibility, especially at population level when targeting those with long-term conditions, it may not be the most effective. Meta-analyses suggest unsupervised exercise is ineffective compared to supervised training at improving health outcomes in a variety of long-term conditions (Umpierre et al., 2011, Vemulapalli et al., 2015, Lacroix et al., 2017, Fennell et al., 2016). There are several possible reasons why unsupervised exercise may be less effective, including poor adherence (referring to performing the recommended number of sessions) and compliance (referring to achieving the recommended duration and intensity) to prescribed exercise, which impacts of the ability of interventions to positively affect clinical outcomes (Shore et al., 2019, Palazzo et al., 2016). Poor adherence has been evident in healthcare settings, including ERS studies (Morgan, 2005, Pavey et al., 2012). Potential reasoning for poor adherence to unsupervised exercise can be traced to a lack of knowledge, lack of personalisation and lack of support from exercise specialists (Morgan et al., 2016a, Bachmann et al., 2018). Hence, effective strategies to overcome these barriers and increase adherence to PA and exercise must be examined.

Modern technological advances hold a potential solution in the form of mobile health (mHealth) technology, encompassing mobile applications, wearable devices and other technologies, to enhance personalised exercise prescription and improve adherence. These

technologies could be used to enable remote support from health professionals or exercise specialists who could provide communication and feedback (e.g., personalised text messages) and provision of instant, individual biometric feedback during exercise (e.g., exercise intensity via heart rate [HR]). mHealth interventions have been used previously in people living with RA, though mostly in relation to self-monitoring disease activity or employed only web-based components (Seppen et al., 2020), in comparison to the present study which uses mobile devices to support an intervention aiming to increase PA. Recent research has shown that mHealth technology can induce significant improvements in PA, via the use of apps and fitness trackers, in both general and clinical populations (Laranjo et al., 2021, Short et al., 2018). Interestingly, self-monitoring and feedback on behaviour have been cited as two of the most effective behaviour change techniques (Michie et al., 2009), both of which can be achieved using modern smartphone apps and activity trackers. Instant feedback on PA via activity trackers can facilitate self-monitoring, as well as capturing acceptably accurate data that can be used to offer feedback on PA behaviour. As such, mHealth technology may offer the most cost effective and versatile method to implement these techniques and bridge the gap between exercise counselling and supervised exercise training to facilitate increases in PA.

Therefore, the primary aim of this study is to assess the effectiveness of an mHealth technology supported intervention to increase PA levels in people living with RA. Secondary outcome measures will assess adherence and compliance to the intervention, and the effect of the intervention on basic clinical outcomes, quality of life and disease activity.

4.2. Methods

4.2.1. Participant characteristics and setting

Fifty people with a clinical diagnosis of RA (Table 1), were recruited between February 2021 and November 2022. Recruitment occurred via advertisements on social media and within the Liverpool University Hospitals NHS Foundation Trust. Inclusion criteria required that participants were between 18-65 years old, had no symptoms of/or established CVD (not including controlled hypertension), no history of previous stroke or myocardial infarction, no musculoskeletal impairment or injury precluding walking, not completing >2 hours of structured exercise per week, no change in RA related medication within 3 months, not currently pregnant or planning pregnancy and access to a smartphone with WiFi or a data plan was also required. All participants were informed of the study protocol verbally and in writing before providing verbal and written consent via HelloSign, in line with Health Research Authority (HRA) advice (Sept 2018). The study was approved by Liverpool John Moores University ethics committee (20/SPS/052) and adhered to the *Declaration of Helsinki*.

4.2.2. Study design

A randomised controlled trial using 1:1 randomisation, whereby participants completed baseline assessments prior to completing a 12-week intervention or 12-weeks of 'conventional care' (designed to mirror the experience of a person with RA). Participants randomised to the *MOTIVATE RA intervention* received a personalised walking intervention delivered via mHealth technology, accompanied with a programme of support messages and basic online educational materials similar to those provided in a conventional care setting. Educational materials alone were provided to participants randomised to receive the *conventional care intervention*. All measurements were repeated upon completion of the intervention. All participants were also invited to take part in an optional follow up 3

months following the completion of the intervention. If participants opted in, then they completed all assessments at this third timepoint.

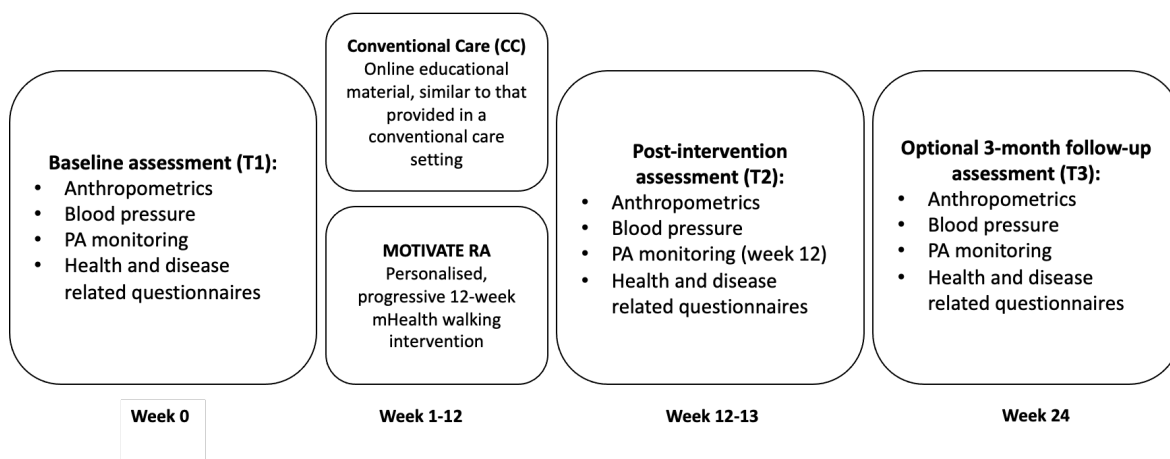


Figure 4.1. Protocol schematic.

4.2.3. Screening, randomisation and blinding

Following an expression of interest, potential participants were screened against eligibility criteria during an initial meeting which took place via telephone or conference call (Zoom Video Communications Inc., 2016). Participants who wished to take part signed written consent, virtually, as described previously. Participants were randomly allocated, using a computer-generated sequence, to either the MOTIVATE RA group ($n=25$) or conventional care (CC) group ($n=25$). Randomisation was performed by an independent researcher. Due to the logistics of posting equipment, participants were notified of their group via email prior to the baseline testing. By design, the researcher and participants were aware of the group allocation.

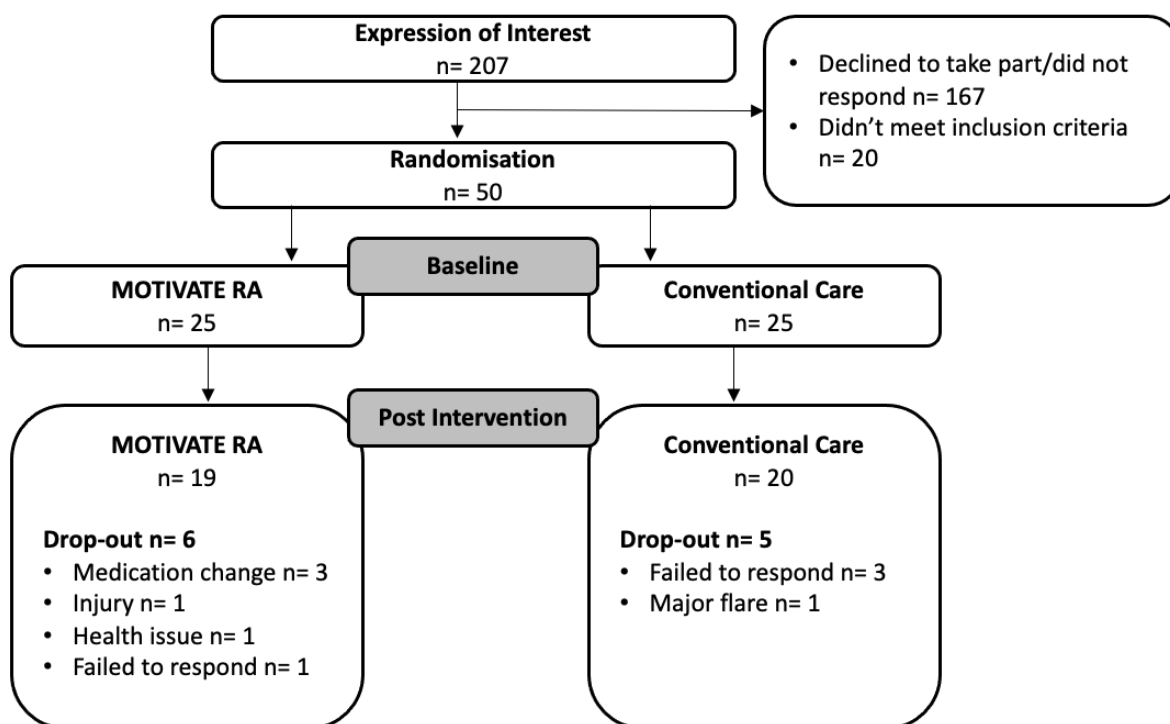


Figure 4.2. Participant consort diagram.

4.2.4. Interventions

Conventional Care group

Participants in the CC group had access to basic online educational materials (accessed via a website), similar to that which is provided in a conventional care setting. These resources included information on the government PA guidelines, recommendations on how to increase and maintain PA and government guidance on PA for those with long-term conditions. No further PA support was provided by the research team throughout the duration of the 12-week intervention period.

MOTIVATE RA intervention group

The MOTIVATE RA group received a multi-component intervention combining three elements: a 12-week personalised, progressive walking programme delivered using mHealth technology, support text messages and online educational materials. Three

specific mHealth apparatus were used; i. a wrist worn fitness watch (Polar Ignite, featuring a 3D accelerometer), ii. a smartphone app (Polar Flow) and iii. a coaching platform (Polar Flow for Coach) used by the research team to deliver and monitor the walking programme. All these elements were utilised synchronously, allowing for data to be transferred between platforms.

Personalised, progressive 12-week walking programme: During a programme planning meeting, participants worked with a member of the research team (DB) to devise and plan a progressive 12-week walking programme that was to be delivered remotely via the use of mHealth technology. Specifically, participants were prescribed a basic 12-week progressive walking programme, with an aim of reaching 150 minutes of MVPA per week by the end of the 12-week intervention period. Participants discussed, with the researcher, how many walks they wished to complete per week and the duration of these walks. With this information the plan was then adapted, as required, and agreed upon. Participants were encouraged to build a plan that steadily progressed up to 150 minutes of MVPA by week 12. All participants were given the goal of remaining within the '*goal HR zone*' for the duration of all walks, this was set at 60%-80% of maximum HR, in line with methods commonly used to prescribe moderate-to-vigorous intensity exercise (MacIntosh et al., 2021). Participants were instructed to try to not drop below this goal zone, measured using a Polar watch, but that they could exceed it if they wished.

Polar Flow for Coach: All participants assigned to the MOTIVATE RA group were managed by a researcher via the Polar Flow for Coach online platform. This enabled the researcher to programme the agreed upon walking programme. The researcher programmed each individual walk, specifying the duration and intensity (measured via HR). These walks were available as pre-programmed sessions on the participants' fitness watch that they could start and complete on any day in the given week of the programme. Throughout the

intervention the online platform provided access to participants session data including HR traces, rate of perceived exertion (RPE: CR-10 scale ratings) (Borg, 1998) and individual written comments from each session provided by the participants, which they were encouraged to complete.

Polar Flow – Sync & Analyse: Participants used the Polar Flow mobile application to view/track their sessions and achievements. It was possible for participants to edit their programme within Polar Flow, for example changing the day of the week of their walk, to fit their schedule. All data recorded by the fitness watch was available in Polar Flow; participants were able to rate each walk from 1-10 on an RPE scale and provide written comments on their session.

Wrist worn fitness watch (Polar Ignite): Participants were given a *Polar Ignite* fitness watch, which features a triaxial accelerometer and optical HR monitor, to use for the duration of the programme which they could either wear continuously throughout the day or wear for completing each walk. Participants were able to access pre-programmed walks via their watch, which were designed and programmed by a member of the research team. The prescribed duration and intensity, via HR zones, was displayed in real time on the watch throughout walking sessions. The watch provided live visual and haptic feedback and alerts, coaching participants to execute the session as prescribed (i.e., remaining in the goal HR zone for the duration of the walk). If participants decided not to select the pre-programmed walk (or mistakenly did not select it), the watch still provided live visual feedback on duration and intensity but there would be no set parameters for this. All data collected by the fitness watch was transferred to the participants Polar Flow app via a simple syncing process.

PA Support Messages: Participants were asked to provide an RPE and written comments following all walks, using the app. The comment was to relate to the appropriateness of walk duration and intensity and their enjoyment of the session, as well as any additional contextual information. For the first 6-weeks of the programme a researcher used this feedback, along with data feedback on HR from the Polar Flow for Coach platform, to send a personalised support message in response to every planned walk. The researcher offered feedback on how well the participant maintained the set intensity of the session as well as general feedback, support, and motivation. Participants also had the opportunity to respond to these messages to receive further feedback/communication with the researcher. If required, further adjustments to the programme could be made at any time according to the feedback provided. After week 6 of the intervention, these support messages were reduced to one per week and offered feedback on each session, as well as the week as whole.

Online educational materials: Participants had access to the same basic online education materials (accessed via a website) as mentioned above in the CC intervention. Participants in the mHealth intervention also had access to instructional guides for the mHealth technology elements both in written and video format.

Optional refresher meeting: Participants were offered an optional refresher meeting at week 3 of the intervention. In this meeting they could ask any questions about the programme or re-cap the use of the mHealth technology elements. Participants could also contact the research team at any time during the intervention for assistance.

The design of the MOTIVATE RA programme was informed by social cognitive theory (Bandura, 1986). Moreover, specific intervention components were focussed on Michie and colleagues' taxonomy of behaviour change technique (Michie et al., 2011) categories,

such as “Goals and Planning” (e.g., target heart rate zone and duration) and “Feedback and Monitoring” (e.g., PA support messages) designed to promote long-term adherence to PA and exercise. These mechanisms were considered appropriate to improve competence to be physically active whilst enhancing uptake and maintenance of PA.

4.2.5. Measurement outcomes

Pre-intervention baseline testing (T1): One week prior to proposed baseline testing date participants were provided with all necessary equipment and detailed instructions in a testing kit (via postal delivery direct to participants preferred address). Participants also had access to testing resources and videos online on the study website. Testing resources included step-by-step written instruction for each measurement available on the website and testing booklet, along with an instructional video depicting the measurements being taken. The testing kit included a BP monitor, measuring tape, PA monitor, *Polar Ignite* fitness watch (MOTIVATE RA only) and questionnaires (sent via email). Participants had a telephone/video call with a member of the research team the day before testing to discuss the protocol and answer participant questions. On the day of testing a member of the research team was available to provide remote assistance, if needed. All assessments were completed following an overnight fast, having abstained from caffeine and alcohol for 12 hours, and vigorous exercise for 24 hours. Data (anthropometrics and BP) were sent to the research team using an online reporting form (www.googleforms.co.uk).

Anthropometrics: Participants were provided a tape measure (Seca 201, Germany) and electronic scales (Salter, UK). Participants used the tape measure to record height. Waist circumference was measured in triplicate at the level of the umbilicus. Previous work suggests a strong correlation between self-measured and technician-measured height and body mass (Kushi et al., 1988) and waist circumference, measured at the umbilicus (Brown et al., 2018).

Blood pressure: Participants were provided an automated BP monitor, validated by the British and Irish Hypertension Society (UK, Salter BPA-9200-GB; CA, Bios BD215) and measured BP in triplicate following 10 minutes of seated rest. Self-measured BP is a validated approach for monitoring BP, endorsed by the American Heart Association and American Medical Association (Shimbo et al., 2020a).

Physical Activity Monitoring: PA was monitored using the GT9X tri-axial accelerometer (ActiGraph, Pensacola, FL, USA). Participants wore the accelerometer on their non-dominant wrist for 7 consecutive days. A recording window of 7 days, starting at midnight on the day of baseline and post-intervention assessments was utilised. The accelerometer was pre-set to record at 30Hz to account for transit in the post, while optimising the battery life of the device. Accelerometer data was downloaded using ActiLife version 6.11.9 (ActiGraph, Pensacola, FL, USA) and analysed using the open-source R software package, GGIR (R package for accelerometry) beta v1.6-1 (<https://cran.r-project.org/web/packages/GGIR/index.html>). GGIR performs autocalibration with the reference of local gravity (van Hees et al., 2014a). Raw acceleration data were used to compute Euclidean norm minus one (ENMO in mg) (van Hees et al., 2013b). Data were analysed from the first to the final midnight using 5-second epochs. Participants were included in the main analysis if they achieved a minimum of 10 hours of wear time for a minimum of 4 days, including at least 1 weekend day. Non-wear was detected if the standard deviation (SD) of two axes was < 13 mg with a range of < 50 mg in windows of 60 minutes. Time spent in activity intensities was established using published thresholds (Hildebrand et al., 2014, Hildebrand et al., 2017). Sedentary time was defined as time accumulated below 45 mg, light PA was defined as ≥ 46 mg and <100 mg, moderate PA was defined as ≥ 101 mg and <428 mg, and vigorous PA was defined as ≥ 429 mg. The following metrics of PA were assessed, moderate-to-vigorous PA (MVPA), number of weekly minutes

of sedentary time, total, light, moderate, vigorous and MVPA, steps per day and average accelerations per day.

Questionnaires: Participants completed online versions of i. self-reported joint count and medication ii. SF-36 health survey (Ware Jr, 2000), iii. RADAI-5 (Leeb et al., 2008), iv. FACIT fatigue scale (Webster et al., 2003), v. PHQ-8 (Kroenke et al., 2009) and vi. the Godin Leisure Time Exercise Questionnaire (Godin and Shephard, 1985) (GLTEQ – completed monthly).

Self-reported joint count was reported by participants totalling the number of swollen and tender joints from the 28 joints included in the disease activity score for RA. The SF-36 health survey, designed to measure health at an individual level in clinical practice and research, assessed a series of quality-of-life measures that can be divided into physical and mental scores. RADAI-5, a short, five question questionnaire was employed to give another measure of RA disease activity based on participant reported experiences and symptoms. The FACIT fatigue scale, a 13-item measure of self-reported fatigue, was used to assess level of fatigue within participants as this is a common symptom of RA. PHQ-8 assessed the level of depression, another common symptom of RA. Finally, the GLTEQ was employed to give a self-reported indication of how much exercise participants were completing. Participants were also asked to report all current medications.

All questionnaires and surveys were completed online using Google Docs (<https://www.google.co.uk/docs>), a secure web application for building, sharing, and managing online documents including questionnaires and surveys. Participants were encouraged to complete the questionnaires immediately following their self-assessment. If questionnaires were not completed, reminders were sent after three and seven days.

Post-intervention testing (T2): Measurements taken post-intervention were identical to the stated above. Participants were asked to wear the PA monitor for the final week of the intervention (week 12).

Three month follow up testing (T3): All participants could take part in an optional three month follow up assessment. If participants choose to take part, they completed the same identical measurements as stated above.

MOTIVATE RA intervention adherence and compliance: Using data uploaded to www.polarflow.com the following metrics of adherence and compliance were assessed (Hesketh et al., 2021b):

- Drop-off: defined as the week during which participants no longer completed any walking sessions.
- Programme adherence: defined as the % of prescribed sessions completed, where 100% adherence was completing all prescribed sessions (usually 36 sessions, 3 sessions/week over 12 weeks).
- Compliance: Refers to the achievement of both a prescribed duration and intensity. The duration was adjusted for the exercise intensity to produce a HR physical activity score ($HRPAS = \text{min} * \%HR_{\text{max}}$) for each session (Miller et al., 2014). If the session HRPAS was equal or greater than the prescribed HRPAS, the session was compliant.

4.2.6. Statistical analysis

Analysis was performed using Statistical Package for Social Sciences (SPSS) [Version 29; SPSS Inc., Chicago, IL]. Visual inspection of histograms and the Shapiro-Wilk test was employed to assess the normality of the unstandardised residuals. Baseline characteristics between conditions were analysed using an independent samples *t*-test. An analysis of

covariance (ANCOVA) was utilised to compare intervention effects between groups at T2, from T1. The dependent variable was each post outcome value, with group as the independent variable. Baseline values for all variables were entered as covariates to control for difference between groups at baseline (Vickers and Altman, 2001). Exploratory analysis was conducted on the three-month follow-up data using a two-way repeated measures ANOVA comparing outcomes between groups at T1, T2 and T3. Follow-up data analysis was conducted on participants who completed all three data collection timepoints, for the MOTIVATE RA group $n = 13$ (health and disease symptom outcomes) and $n = 9$ (PA outcomes), and for the CC group $n = 13$ and 9 respectively. All data are reported in text as mean (95% confidence interval), unless otherwise stated, and statistical significance was delimited at $P \leq 0.05$. Exact P values are cited.

4.3. Results

Between February 2021 and November 2022, $n = 207$ people expressed an interest in the study, of these $n = 187$ were eligible and $n = 50$ participants were recruited. Participants were randomised to MOTIVATE RA ($n = 25$, females $n = 23$) or CC ($n = 25$, females $n = 24$) groups.

There were no significant differences between the groups in terms of their baseline characteristics ($P > 0.05$, Table 1). The MOTIVATE RA group recorded a higher weight (8kg; [95% CI = -3, 19]), BMI (3 kg.m²; [95% CI = -1, 7]) and waist circumference (7cm; [95% CI = -1, 15]) compared to the CC group but these did not reach statistical significance and importantly for BMI, both groups were considered 'overweight', so they shared the same clinical classification

Table 4.1. Baseline participant characteristics (mean $\pm$ SD).

	MOTIVATE RA (n=25)	Conventional Care (n=25)	P value
Age (years)	50 $\pm$ 11	50 $\pm$ 11	0.96
Weight (kg)	80 $\pm$ 21	71 $\pm$ 16	0.14
Height (cm)	165 $\pm$ 8	165 $\pm$ 9	0.94
BMI (kg/m ²)	29 $\pm$ 7	26 $\pm$ 6	0.15
Waist circumference (cm)	93 $\pm$ 15	86 $\pm$ 11	0.07
SBP (mmHg)	116 $\pm$ 15	113 $\pm$ 19	0.53
DBP (mmHg)	79 $\pm$ 8	77 $\pm$ 9	0.28
MAP (mmHg)	98 $\pm$ 11	95 $\pm$ 14	0.40
Medication (n of participants)			
DMARD	16	20	/
Biologic	7	5	/
Anti-TNF	1	4	/

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MA: mean arterial pressure, DMARD; disease modifying anti-rheumatic drug, TNF; tumour necrosis factor.

4.3.1. Physical activity outcomes

There were no significant differences across PA outcomes. The MOTIVATE RA group were performing 103 minutes (95% CI = -17, 224; $P = 0.09$) more MVPA, 85 minutes (95% CI = -22, 193; $P = 0.12$) more moderate PA and 13 minutes (95% CI = -6, 33; $P = 0.18$) more vigorous PA than the CC group at T2, though these differences in time spent in different domains of PA were not deemed significant ($P > 0.05$, Table 3), they do suggest a trend of increase PA in the MOTIVATE RA group.

Average accelerations were observed to be 1.2mg/day (95% CI = -3.5, 5.8; $P = 0.61$) higher in the MOTIVATE RA group than in the CC group, though this did not reach statistical significance.

The GLTEQ questionnaire revealed that the MOTIVATE RA group completed 1 (95% CI = -0, 2; $P = 0.12$) moderate and/or strenuous session more and scored a 4 (95% CI = -5, 14; $P = 0.37$) higher total GLTEQ score compared to the CC group at T2, though these outcomes did not reach statistical significance.

There were no significant differences between groups at T2 for light PA, total PA, sedentary time and steps ($P > 0.05$).

Table 4.2. Physical activity data at baseline and post-intervention where both baseline and post-intervention data are available (per protocol).

	MOTIVATE RA (n= 17)		Conventional Care (n= 14)		Adjusted between group differences ^a	P
	Baseline ^b	Post-intervention ^b	Baseline ^b	Post-intervention ^b		
Physical Activity						
Light PA	869 ± 211	904 ± 222	896 ± 343	987 ± 390	-66 (-255, 123)	0.48
Moderate PA	365 ± 157	433 ± 192	490 ± 237	456 ± 248	85 (-22, 193)	0.12
Vigorous PA	8 ± 13	21 ± 55	7 ± 11	7 ± 7	13 (-6, 33)	0.18
MVPA	373 ± 161	453 ± 221	498 ± 238	463 ± 253	103 (-17, 224)	0.09
Total PA	1238 ± 335	1350 ± 396	1389 ± 551	1447 ± 599	18 (-260, 296)	0.90
Sedentary time	8672 ± 600	8476 ± 673	8382 ± 987	8325 ± 883	92 (-488, 671)	0.75
Steps (steps/day)	9720 ± 2012	10483 ± 2958	10417 ± 2726	10341 ± 2618	679 (-952, 2310)	0.40
Average accelerations (mg/day)	19.4 ± 4.9	21.7 ± 7.3	21.4 ± 6.0	22.0 ± 7.3	1.2 (-3.5, 5.8)	0.61
GLTEQ (moderate & strenuous sessions)*	1 ± 1	3 ± 2	1 ± 2	2 ± 2	1 (-0, 2)	0.12
GLTEQ (total score)*	14 ± 11	26 ± 14	18 ± 17	25 ± 22	4 (-5, 14)	0.37

^aAdjusted mean difference between MOTIVATE RA and Conventional Care after ANCOVA accounting for baseline. ^bBaseline and post-intervention values are unadjusted mean ± SD. *GLTEQ questionnaire was completed by n = 19 (MOTIVATE) and n = 20 (Conventional Care). P-value refers to statistical significance of between-group differences from ANCOVA. MVPA: moderate-to-vigorous physical activity. All physical activity data shown above is minutes per week, unless otherwise stated.

4.3.2. Adherence and compliance

Adherence and compliance to prescribed walking, measured via optical HR monitor (*Polar Ignite*) [Table 2], indicates that participants completed approximately two walking sessions per week, which led to a total adherence to prescribed sessions of 73%. Compliance, assessing whether sessions were completed as prescribed (i.e., within goal heart rate zones) was 67%, rising to 91% when only recorded sessions (i.e., sessions attempted) were included.

Table 4.3. Adherence and compliance assessed by device derived measurement of walking sessions (mean $\pm$ SD).

Outcome	MOTIVATE RA ($n=23$)
Number of sessions per week (n)	1.9 $\pm$ 1.1
Total adherence (% of prescribed)	73 $\pm$ 32
Compliance (% of prescribed sessions completed correctly)	67 $\pm$ 31
Per protocol compliance (% of recorded sessions completed correctly)	91 $\pm$ 11

Intention-to-treat data displayed, except for per-protocol analysis for compliance which included only recorded sessions.

Moderate-to-Vigorous Exercise (MVE)

In the final week of the intervention (week 12) participants in the MOTIVATE RA group completed approximately 87 minutes of MVE (i.e., 60% HRmax or above) during the walking sessions they recorded.

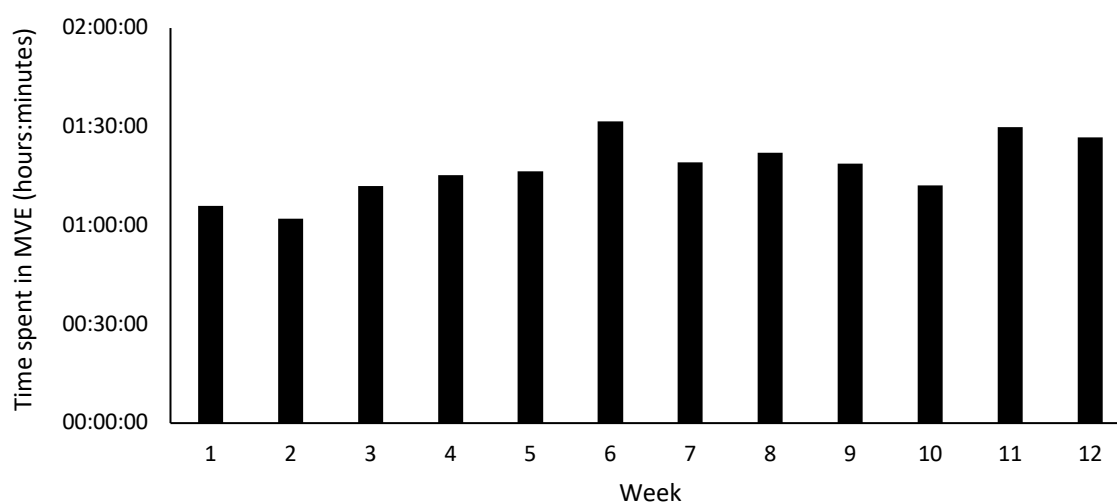


Figure 4.3. Intention-to-treat data for time spent completing MVE (60% HRmax or above) per week during recorded walking sessions.

Participants still completing walking sessions

In the final week of the intervention (week 12), 70% of participants in the MOTIVATE RA group were still completing at least one prescribed walking session per week averaging approximately 87 minutes of prescribed walking.

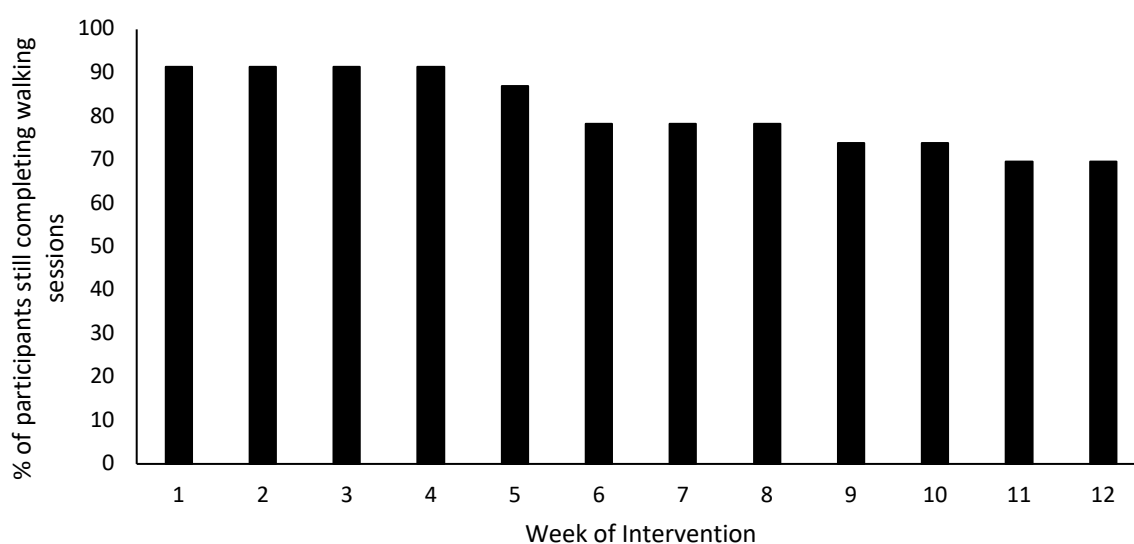


Figure 4.4. Intention-to-treat data for participants still completing at least one walking session per week.

4.3.3. Health and disease symptom related outcomes

There were no significant differences across health and disease symptom related outcomes. The MOTIVATE RA group demonstrated a higher FACIT fatigue scale score, by 4 points (95% CI = -1, 9; $P = 0.14$), compared to the CC group at T2. Similarly, the MOTIVATE RA group also exhibited a lower PHQ-8 depression questionnaire score, by 2 points (95% CI = -4, 1; $P = 0.15$). Finally, the MOTIVATE RA group demonstrated a higher SF36 mental questionnaire component score, by 6 points (95% CI = 3, 14; $P = 0.17$). Though none of these differences reached statistical significance (Table 2), they do suggest a trend of reduced fatigue and improved mental health in the MOTIVATE RA group.

Following the completion of the MOTIVATE RA and CC groups at T2 there was no differences between groups observed in terms of anthropometrics, BP, clinical symptoms and SF-36 physical questionnaire component ($P > 0.05$, Table 2).

Table 4.4. Baseline and post-intervention scores for remotely measured outcomes where both baseline and post-intervention data are available (per protocol)

	<i>MOTIVATE RA</i> (n= 19)		Conventional care (n= 20)		Adjusted between group differences ^a	<i>P</i>
	Baseline ^b	Post-intervention ^b	Baseline ^b	Post-intervention ^b		
Anthropometrics						
Weight (kg)	84 ± 10	83 ± 19	69 ± 12	69 ± 11	-0.97 (-2.82, 0.87)	0.29
BMI (kg.m ²)	31 ± 7	30 ± 7	25 ± 4	25 ± 4	-0.28 (-1.06, 0.48)	0.45
Waist circumference (cm)	95 ± 15	95 ± 14	84 ± 8	83 ± 7	1.79 (-2.41, 5.98)	0.39
Blood Pressure						
SBP (mmHg)	115 ± 13	114 ± 11	111 ± 20	110 ± 15	2.99 (-2.83, 8.81)	0.30
DBP (mmHg)	81 ± 7	78 ± 7	76 ± 9	74 ± 11	0.77 (-4.27, 5.81)	0.76
MAP (mmHg)	98 ± 9	96 ± 8	94 ± 14	92 ± 12	2.09 (-3.01, 7.19)	0.41

Clinical Symptoms						
Self-reported joint count	3 ± 5	4 ± 5	4 ± 5	6 ± 5	-1.08 (-4.02, 1.86)	0.46
RADAI-5	4 ± 2	4 ± 2	4 ± 2	4 ± 2	-0.63 (-1.88, 0.61)	0.31
FACIT	27 ± 13	31 ± 15	32 ± 13	31 ± 9	4.03 (-1.40, 9.47)	0.14
PHQ-8	8 ± 5	6 ± 5	7 ± 7	7 ± 6	-1.80 (-4.30, 0.70)	0.15
SF-36						
Physical (PCS-36)	50 ± 9	54 ± 10	50 ± 9	54 ± 9	-0.35 (-6.00, 5.31)	0.90
Mental (MCS-36)	56 ± 16	65 ± 17	61 ± 19	62 ± 17	5.80 (-2.61, 14.21)	0.17

^aAdjusted mean difference between MOTIVATE RA and Conventional Care after ANCOVA accounting for baseline. ^bBaseline and post-intervention values are unadjusted mean ± SD. P-value refers to statistical significance of between-group differences from ANCOVA. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; RADAI-5: rheumatoid arthritis disease activity score 5; SF-36: 36-Item Short Form Survey; PCS: physical health component score; MCS: mental health component score; FACIT: functional assessment of chronic illness therapy – fatigue scale; PHQ-8: patient health questionnaire depression scale 8.

4.3.4. Three-month follow-up assessment

Health and disease symptom outcomes at three-month follow-up: Exploratory analyses revealed a significant main effect of group for weight, BMI and waist circumference. Weight was greater in the MOTIVATE RA group compared to the CC group (18kg [95% CI = 2, 34]; $P = 0.03$). The MOTIVATE RA group also exhibited greater BMI (6 kg.m² [95% CI = 0, 11]; $P = 0.04$) and waist circumference (15cm [95% CI = 5, 25]; $P = 0.01$) compared to the CC group.

There was also a significant main effect of time for DBP ($P = 0.03$). Specifically, DBP reduced between T1 and T2 (-4 mmHg [95% CI = -0, -7]; $P = 0.04$).

There were no significant group*time interactions identified ($P > 0.05$).

Table 4.5. Three-month follow-up scores for remotely measured outcomes.

	MOTIVATE RA (<i>n</i> = 13)			Conventional Care (<i>n</i> = 13)			Two-way ANOVA, <i>P</i> values		
	Baseline	Post- Intervention	3-month follow-up	Baseline	Post- Intervention	3-month follow-up	Group	Time	Group*Time
Anthropometrics									
Weight (kg)	86 ± 20	84 ± 21	84 ± 21	67 ± 13	68 ± 11	66 ± 11	0.03*	0.06	0.20
BMI (kg.m ²)	31 ± 8	31 ± 7	31 ± 8	25 ± 5	25 ± 4	25 ± 4	0.04*	0.05	0.29
Waist circumference (cm)	97 ± 15	97 ± 14	97 ± 15	84 ± 7	81 ± 6	80 ± 6	0.01*	0.10	0.46
Blood Pressure									
SBP (mmHg)	117 ± 14	115 ± 13	117 ± 17	114 ± 22	108 ± 15	107 ± 14	0.24	0.21	0.39
DBP (mmHg)	80 ± 8	78 ± 6	77 ± 11	75 ± 10	70 ± 9	74 ± 7	0.07	0.03*	0.34
MAP (mmHg)	98 ± 10	97 ± 9	97 ± 13	95 ± 15	89 ± 11	90 ± 10	0.14	0.09	0.58
Clinical Symptoms									
Self-reported joint count	2 ± 3	4 ± 5	5 ± 7	4 ± 4	6 ± 6	5 ± 6	0.22	0.23	0.20
RADAI-5	3 ± 2	4 ± 3	4 ± 3	3 ± 2	4 ± 2	4 ± 2	0.84	0.36	0.93
FACIT	29 ± 13	33 ± 15	34 ± 13	35 ± 12	34 ± 9	32 ± 11	0.32	0.86	0.60

PHQ-8	8 ± 5	6 ± 5	6 ± 7	6 ± 6	6 ± 5	6 ± 6	0.60	0.16	0.44
SF-36									
Physical (PCS-36)	51 ± 9	54 ± 10	52 ± 12	50 ± 9	54 ± 8	52 ± 9	0.93	0.16	0.94
Mental (MCS-36)	60 ± 16	66 ± 17	64 ± 17	64 ± 19	65 ± 17	59 ± 17	0.93	0.42	0.45

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; RADAI-5: rheumatoid arthritis disease activity score 5; SF-36: 36-Item Short Form Survey; PCS: physical health component score; MCS: mental health component score; FACIT: functional assessment of chronic illness therapy – fatigue scale; PHQ-8: patient health questionnaire depression scale 8.

Physical activity outcomes at three-month follow-up: Exploratory analysis revealed a significant main effect of group for light PA and total PA. Light PA was lower in the MOTIVATE RA group compared to the CC group (-175 min [95% CI = -323, -27]; $P = 0.03$). The MOTIVATE RA group also had lower total PA in comparison to the CC group (-372 [95% CI = -724, -21]; $P = 0.04$).

There was also a significant main effect of time for GLTEQ moderate and strenuous sessions ($P = 0.03$). Specifically, GLTEQ moderate and strenuous sessions increased between T1 and T2 (2, 95% CI = 1, 3, $P < 0.01$).

There were no significant group*time interactions ($P > 0.05$)

Table 4.6. Physical activity data at three-month follow-up.

	MOTIVATE RA (<i>n</i> = 9)			Conventional Care (<i>n</i> = 10)			<i>P</i> values		
	Baseline	Post-Intervention	3-month follow-up	Baseline	Post-Intervention	3-month follow-up	Group	Time	Group* Time
Physical Activity									
Light PA	867 ± 227	948 ± 224	891 ± 250	1000 ± 286	1101 ± 372	1060 ± 303	0.03*	0.22	0.84
Moderate PA	350 ± 148	455 ± 189	380 ± 249	571 ± 210	531 ± 250	607 ± 317	0.10	0.35	0.16
Vigorous PA	9 ± 17	32 ± 75	39 ± 87	10 ± 13	8 ± 8	7 ± 9	0.38	0.24	0.28
MVPA	359 ± 155	487 ± 240	390 ± 263	581 ± 207	539 ± 254	608 ± 315	0.14	0.34	0.11
Total PA	1222 ± 332	1427 ± 381	1281 ± 378	1575 ± 452	1635 ± 567	1668 ± 565	0.04*	0.21	0.54
Sedentary time	8858 ± 332	8493 ± 684	8159 ± 1369	8505 ± 452	8157 ± 883	8268 ± 725	0.31	0.15	0.50
Steps (steps/day)	9575 ± 2144	10980 ± 2441	9931 ± 2257	11525 ± 1703	11183 ± 2334	11954 ± 3476	0.42	0.58	0.14
Average accelerations (mg/day)	18.8 ± 4.7	23.1 ± 8.2	22.9 ± 7.9	23.2 ± 5.	24.4 ± 6.9	24.4 ± 7.4	0.30	0.10	0.49
GLTEQ (moderate & strenuous sessions)*	1 ± 1	3 ± 2	2 ± 3	1 ± 2	2 ± 2	2 ± 2	0.31	0.02*	0.50

GLTEQ (total score)*	13 ± 11	24 ± 13	23 ± 19	20 ± 20	27 ± 26	30 ± 27	0.45	0.06	0.72
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MVPA: moderate-to-vigorous physical activity. All physical activity data shown above is minutes per week, unless otherwise stated.

4.4. Discussion

These novel data demonstrate, for the first time, the promising potential of mHealth supported interventions to increase PA in people living with RA. Meaningful increases in MVPA and vigorous PA were observed in the MOTIVATE RA group in comparison to the conventional care group. Whilst these differences between groups did not reach statistical significance, a 103-minute difference in MVPA between groups constitutes a substantial increase in PA. Moreover, average accelerations were observed to be 1.2 mg/day higher in the MOTIVATE RA group, with a ~1 mg/day increase in average accelerations deemed as the minimum clinically important difference (MCID) for inactive adults (Rowlands et al., 2020). One of two secondary aims of the study was to assess the effect of the intervention on basic clinical outcomes, quality of life and disease activity. There were no differences between the MOTIVATE RA group compared to the conventional care group in any of these outcomes, though there were small (non-significant) improvements in fatigue and mental wellbeing in the MOTIVATE RA group. Lastly, the study aimed to assess adherence and compliance to the intervention; these data demonstrated the high level of suitability of the MOTIVATE RA intervention for people living with RA and unveiled great potential for mHealth supported interventions in this population.

It is clear from the data that the MOTIVATE RA intervention increased PA levels in people living with RA in comparison to the increase observed in the conventional care pathway (103 minutes). It is challenging to make direct comparisons with other studies attempting to increase PA due to differences in methodology. Despite a vast array of research studies examining the effects of exercise and PA on RA, very few studies have explored PA behaviour change (Cramp et al., 2013, Larkin et al., 2015). In studies that have examined the ability of interventions to increase PA in people living with RA, questionnaires are most often used

(Brodin et al., 2008, Mayoux-Benhamou et al., 2008, Knittle et al., 2015). Only a few have studies utilised devices that derive objective measures of PA, including accelerometry (Van den Berg et al., 2006, Gilbert et al., 2018) and pedometers (Katz et al., 2018, Baxter et al., 2016b). However, in line with the findings of the present study, a recent systematic review and meta-analysis reported that interventions utilising apps and trackers were effective in promoting PA in adults (Laranjo et al., 2021). Moreover, the present study builds upon previous research within this thesis (*Chapter 3*), whereby feasibility data suggested that an mHealth supported exercise intervention could have a positive effect on exercise behaviour of inactive adults (Bannell et al., 2023). This potential has translated into an increase in PA in a high-risk clinical population, which could result in a meaningful clinical management tool following further exploration and research. Furthermore, a recent systematic review and meta-analysis assessed the use of wearable activity trackers to improve PA in patients with rheumatic and musculoskeletal disease and observed an average increase of 16 minutes of MVPA, though only three (all with patients with osteoarthritis) of the 17 studies included assessed MVPA (Davergne et al., 2019). The growing evidence appears to be strengthening the hypothesis that PA is an important lifestyle factor in the management of RA, and emphasises the promising potential of mHealth supported PA interventions in people living with RA.

Notably the present study also demonstrated a 1.2 mg/day difference between groups as well as a total increase of 2.3 mg/day in the MOTIVATE RA group compared with a 0.6 mg/day increase in the conventional care group. Recent research has identified that a ~1 mg increase in daily average acceleration using wrist-worn accelerometers is the MCID for inactive adults (Rowlands et al., 2020). Moreover, it was demonstrated that higher average acceleration (per 1 mg) was associated with a 5.2% lower risk of a cardiovascular event in inactive adults using

data from the UK biobank (Rowlands et al., 2020). Thus, the MOTIVATE RA intervention could potentially have decreased the risk of a cardiovascular event by $\geq 10\%$ given that people with RA are more likely to be inactive. These prognostic data indicate that the lack of statistical significance identified may be overshadowed by what constitutes a clinically meaningful change as such, future research should assess the impact of increased average accelerations specifically in people living with RA. Meanwhile, 500 steps/day has been proposed as the MCID in ambulatory activity needed to convey reduced risk of CVD in inactive adults (Yates et al., 2019), with studies in inactive older women and US adults suggesting that a 500 step/day difference in activity is associated with $\sim 8\text{-}9\%$ lower risk of all-cause mortality. In the present study the MOTIVATE RA group increased their step count by 679 more steps/day compared to the conventional care group. This further evidences that the MOTIVATE RA intervention elicited clinically meaningful behaviour change that could reduce CVD risk and all-cause mortality.

The MOTIVATE RA intervention did not elicit any greater changes than conventional care in basic clinical outcomes, quality of life or disease activity, which is somewhat unsurprising given the short period of the intervention; a finding that is reflected in previous research detailed in this thesis (*Chapter 3*; (Bannell et al., 2023)). Despite this there was evidence of small improvements in mental health outcomes in the MOTIVATE RA group in comparison to CC, including improvements in overall mental health and reductions in fatigue and depression. Given that depression is two times more prevalent in people living with RA (Lwin et al., 2020) it is encouraging that the current 12-week walking intervention was able to elicit small improvements in mental health outcomes. However, future research should incorporate

specific interventional components to seek greater improvements in mental health in people living with RA.

It is of the utmost importance that interventions seeking to increase PA and exercise in insufficiently active individuals, that are often recommended unsupervised exercise and PA through ERS (Rowley et al., 2021), promote and encourage high levels of adherence and compliance. Adherence in the MOTIVATE RA group based on sessions captured via the *Polar Ignite* wrist worn fitness watch was 73% and compliance in performing the walking sessions within the correct goal heart rate zone was 91% (for all attempted sessions). These data indicate greater levels of adherence in comparison to previously published data. For example, an ERS conducted in high-risk clinical populations reported 39% adherence in a home-based high intensity interval training intervention and 48% in a traditional moderate intensity continuous training ERS intervention (Hesketh et al., 2021b). Furthermore, Taylor et al. (1998) reported a 45% attendance rate (measured via gym sign in) to a gym-based UK ERS. Interestingly, a systematic review by Pavey et al. (2012) found large variability in adherence rates to ERS ranging from 12-93%, however it was noted this was in part due to different definitions of adherence being utilised, an observation that supports the need for the study outlined in *Chapter 6*. The high compliance rate (91%) of the MOTIVATE RA intervention was in line with previous findings from other moderate intensity ERS in at risk individuals (Hesketh et al., 2021b). Moreover, the high level of compliance in the MOTIVATE RA intervention highlights both that the intervention was successful in encouraging people living with RA to complete MVPA and that the intervention itself is feasible for people living with RA.

Further evidence of this is demonstrated by the fact that 70% of participants were still completing at least one walking session per week, as well as spending ~87 minutes completing

MVE (captured from recorded walking sessions) at the end of the 12-week intervention period. Collectively, these data demonstrate the potential of mHealth supported interventions to increase PA in people living with RA and suggest that this mode of intervention may be effective in alleviating barriers to unsupervised ERS participation such as lack of support and lack of personalisation (Morgan et al., 2016a) and promoting facilitators to PA and exercise in people living with RA such as support from HCPs and social support (Veldhuijzen van Zanten et al., 2015b). Taken together, the current data therefore suggest, for the first time, that an mHealth supported intervention is both feasible and acceptable to the RA community.

The present study did not reveal any group x time interactions when assessing the three-month follow-up data for health and PA outcomes, though this was an optional assessment point and therefore only completed by a subset of participants ($n = 13$). Resultantly, it is difficult to draw any conclusion from these data. The follow-up assessment did indicate that upon cessation of the MOTIVATE RA intervention there was a decline (-97 minutes) in MVPA, though this was still 30 minutes above the MVPA recorded at T1 (baseline). This indicates that once intervention support ceases, participants were essentially back within the conventional care pathway, and habitual PA reflects this. Interestingly, vigorous PA remained high in the MOTIVATE RA group at T3 (3-month follow-up assessment), which suggests a potential increase in confidence in completing strenuous activity. In comparison, the CC group levels of PA increased slightly at the follow-up assessment. This is an unexpected finding and could indicate the influence of COVID-19 restrictions (Institute for Government, 2021) which were in a constant state of flux during this study, on the PA levels of participants within the study. Future research should seek to include follow-up assessments in order to assess long term behaviour change more accurately.

4.4.1. Limitations

The study was not without limitations, the first of which was that the study was conducted between February 2021 and November 2022 during in which time COVID-19 restrictions imposed by the UK government fluctuated which may have affected participants ability and confidence to complete walking sessions, especially given that the RA community were classed as vulnerable due to being immunosuppressed (Institute for Government, 2021). A further limitation is the lack of a comparison in adherence and compliance due to having no HR monitor recorded data for the conventional care group. The conventional care group was designed to provide similar materials to that which would be provided in a conventional care setting, which would not include a HR monitoring device. Finally, health inequality is a prominent and growing issue in the UK (Heaslip et al., 2022), and the present study did not collect demographic data or protected characteristics meaning we are unable to assess the reach of the MOTIVATE RA intervention.

4.4.2. Conclusion

This study demonstrates that mHealth technology supported interventions are feasible and acceptable for people living with RA and these preliminary data further indicate that such interventions may elicit clinically meaningful change, via increases in MVPA. Though there were no statistically significant intervention effects on PA and health outcomes. Future studies should seek to assess longer intervention periods to try to maximise health/disease related outcomes.

**CHAPTER 5: EXPLORING THE IMPACT OF
RHEUMATOID ARTHRITIS ON THE MICRO-,
MACRO- AND CEREBROVASCULAR
FUNCTION**

5.1. Introduction

RA is a chronic auto-immune disease characterised by functional disability, pain, fatigue and can ultimately lead to joint destruction (Hammam et al., 2019). RA also leads to systemic manifestations and complications including pulmonary, neurological, musculoskeletal and cardiovascular problems (Kim and Suh, 2020, Figus et al., 2021). Despite this wide array of concomitant complication, cardiovascular disease (CVD) represents the primary cause of mortality in people living with RA (Kitas and Gabriel, 2011), with ~50% increased CVD risk compared to the general population (Agca et al., 2017). Those living with RA present two-fold increased risk of myocardial infarction (Choy et al., 2014) and two-to-three-fold increased risk of stroke (Nadareishvili et al., 2008) when compared to healthy individuals (Solomon et al., 2003).

The increased cardiovascular burden observed within this population is not only related to the prevalence of traditional cardiovascular risk factors (e.g., physical inactivity, hypertension, hypercholesterolemia, diabetes, smoking) (Baghdadi et al., 2015); it may also be partially attributed to direct effects of inflammation on the vasculature (Skeoch and Bruce, 2015, Alkaabi et al., 2003b, Bordy et al., 2018), which can lead to changes in vascular structure and function that may contribute to the development of atherosclerosis (Skeoch and Bruce, 2015). These inflammatory-driven alterations in dilatory capacity could occur in both the large and small blood vessels throughout the body and brain (Alkaabi et al., 2003b, Bordy et al., 2018, Skeoch and Bruce, 2015). The current level of understanding of vascular function in various vascular beds (e.g., small and large blood vessels or central and peripheral vascular beds) in people living with RA is still unclear.

There is a complex and interrelated relationship between the systematic inflammation seen in RA, CVD risk factors and vascular function. A recent cohort study demonstrated that 70% of CVD events in RA patients could be attributed to CVD risk factors and RA-related risk factors (Crowson et al., 2018). The chronic inflammatory process in rheumatoid joints, that can also affect other organs and tissues, shares some similarities with the inflammatory process in the atherosclerotic blood vessels of CVD (Sandoo et al., 2011b). Concentrations of pro-inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF- α) are raised in both conditions (Stevens et al., 2005, Libby, 2008). These inflammatory molecules have been associated with increased CVD risk in the general population (Ridker et al., 2000), and can aggravate both traditional (e.g., insulin resistance) and non-traditional (e.g., oxidative stress) CVD risk factors (Libby, 2008). These interrelated factors suggest that the systemic inflammation exhibited in RA could contribute to the acceleration of atherogenesis (Pasceri and Yeh, 1999, Manzi and Wasko, 2000). Inflammation itself has a direct effect upon the vasculature (Skeoch and Bruce, 2015, Bordy et al., 2018) leading to changes in vascular properties that precede the development of atherosclerosis (Skeoch and Bruce, 2015).

The development of CVD in people with RA may involve changes in the vasculature across varying levels. Alterations in vascular structure and function play a key role in the pathophysiology of CVDs in RA. For instance, development of atherosclerosis may be preceded by negative adaptations in the macro- and microvasculature. Studies have postulated that the synthesis of NO, vital for regulating vascular tone, may be reduced due to the presence of inflammatory molecules, therefore, having a damaging effect on the endothelium and causing endothelial cell dysfunction (Clapp et al., 2004). Endothelial dysfunction in micro- and

macrocirculations is seen as an early marker for atherosclerosis in many diseases, including RA, as well as the general population (Skeoch and Bruce, 2015, Bordy et al., 2018). Endothelial dysfunction has been shown in people with RA across both the micro- and macrovasculature (Arosio et al., 2007, Sandoo et al., 2011a), but it has been noted that they are independent of each other (Sandoo et al., 2011a). Thus, highlighting the importance of assessing vascular function across multiple vascular beds, including those that have been less investigated.

In the macrovasculature, FMD has been used to quantify endothelial (dys)function (Thijssen et al., 2019) and has been shown to have an inverse association with future cardiovascular events (Ras et al., 2013). A meta-analysis revealed that for every 1% increase in FMD, the risk of experiencing a CVD event decreases by 13% (Inaba et al., 2010). Thus, FMD has been proposed as useful precursor to cardiovascular risk factor assessment, showing strong prognostic relevance (Green et al., 2011). Previous literature is equivocal, though most report reduced FMD% in RA compared to non-RA populations (Xu et al., 2017, Fan et al., 2012, Di Minno et al., 2015), whilst some report no statistical differences (Van Doornum et al., 2003). Although not fully consistent, FMD can be a valuable tool to assess endothelial dysfunction in this population, especially given it is potentially one of the earliest manifestations of CVD that is reversible (Temiz et al., 2015).

It is also important to note that there may also be consequences for less investigated vascular beds in RA, such as the cerebral vasculature. Cerebrovascular disease is the most common life-threatening neurological condition encompassing all disorders where an area of the brain is affected by ischemia or bleeding. This can occur when cerebral blood vessels are involved in a pathological process/event (e.g., stroke). Research has demonstrated that people living with RA are more susceptible to cardio-cerebrovascular events such as stroke. For example,

Lindhardsen et al. (2012) reported that RA patients had a 30% increased risk of stroke compared to non-RA populations. Meanwhile, data from a survey paper indicated that RA patients are more susceptible to morbidity from cardio-cerebrovascular disease (CCVD) when compared with osteoarthritis patients (Wolfe et al., 2003). There is also evidence, though rare, of isolated cerebral vasculitis in RA – which usually leads to patient death (Pons et al., 2010). Cerebrovascular function is often measured using TCD, which provides information on the functional status of the cerebral blood vessels. The first of two commonly employed measurement techniques is cerebrovascular reactivity to CO₂ which assess the relationship between PaCO₂ and CBF. A rise in CBF as a result of increased PaCO₂ is viewed as a defensive mechanism to help remove CO₂ from brain tissue (Ainslie and Duffin, 2009). The second is the measurement of cerebral autoregulation, classified as another defensive mechanism to protect the brain against hypo- or hyperperfusion (Novak et al., 1998). Dynamic cerebral autoregulation (dCA) as measured in this study, allows for the assessment of CA that best reflects BP oscillations experienced during daily tasks. In tandem, these measurements give an indication of cerebrovascular health. This is important as despite emerging evidence of cerebrovascular disease in RA (Wiseman et al., 2016), little is known about the mechanisms underlying the greater cerebrovascular risk in RA. To our knowledge a vital mechanism of cerebrovascular control, cerebral autoregulation, is yet to be explored within the RA population, despite knowing it is adversely affected in other clinical populations such as type 2 diabetes (Van Halm et al., 2009).

The aim of this study was therefore to further explore the impact of RA on micro-, macro- and cerebrovascular function in comparison to matched controls via the concurrent assessment of vascular function across the vasculature tree. A key novel aspect of this study is the parallel

assessment of vascular function across large and small vessels but also the brain, in order to provide an overall picture of vascular function in RA. The hypothesis of this study expects people living with RA to present with reduced vascular function across the vasculature tree.

5.2. Methods

5.2.1. Participant characteristics

Seven females with a clinical diagnosis of RA and 8 female non-RA control participants (Table 1) were recruited to undergo a battery of vascular assessments. Inclusion criteria required that participants in the RA group be aged between 18 and 70 years with a clinical diagnosis of RA, were free from symptoms of or established CVD (except controlled hypertension), no previous stroke or myocardial infarction, no history of diabetes, respiratory or chronic kidney disease, alcohol consumption <14 units per week, no regular medication changes in the previous three months and not currently pregnant. Inclusion criteria for the control group was as above, except for the presence of a clinical RA diagnosis. All participants were clearly informed of the study protocol verbally and in writing before providing verbal and written consent. The study was approved by the NHS Health Research Authority, Northwest – Liverpool Central Research Ethics Committee (19/NW/0706, 266102) and adhered to the standards set out in the *Declaration of Helsinki*.

5.2.2. Study design

An exploratory pilot trial whereby all participants attended the laboratory on one occasion to complete a battery of vascular assessments. The experimental visit was performed at the same time of day for all participants, who had been fasted overnight (12 hours) and abstained from alcohol and strenuous exercise for 24 hours, as well as caffeine for 12 hours. All participants completed the battery of vascular assessments in the following order; brachial FMD and upper

limb post-occlusive reactive hyperaemia LDF simultaneously, femoral FMD and lower limb LDF simultaneously, cerebrovascular reactivity (CVR) and cerebral autoregulation (CA).

5.2.3. Measurements

Anthropometrics: Height and weight were recorded using a stadiometer (Seca, Hamburg, Germany) and digital scales (Seca, Hamburg, Germany), respectively. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Cardiovascular measurements:

Brachial and femoral artery endothelial function: Brachial and femoral artery endothelial function was assessed using the FMD technique, strictly following the most recent guidelines (Thijssen et al., 2019). Briefly, images of the brachial artery were acquired using high-resolution ultrasound (T3300; Terason, Burlington, MA). During FMD of the brachial artery, diameter, flow and shear stress were measured for one minute prior to and three minutes following a five minute period of forearm ischemia, via cuff inflation (D.E. Hokanson, Bellevue, WA) (Thijssen et al., 2019). The femoral artery was assessed at a separate time point with diameter, flow and shear stress measured for one minute prior to and five minutes following a five minute period of upper leg ischemia, via cuff inflation (Hokanson E20/AG101 Rapid Cuff Inflation System, D. E. Hokanson, Inc., Bellevue, Washington, USA) (Thijssen et al., 2019). Analysis was performed by a researcher blinded to the group allocation (using a single blinded coding- randomised procedure) and using custom designed edge-detection and wall-tracking software, which is largely independent of investigator bias; previous articles contain detailed descriptions of this analytical approach (Black et al., 2008, Woodman et al., 2001). Reproducibility of diameter measurements using this semi-automated software is significantly

better than manual methods, significantly reduces observer error, and possesses within-day coefficient of variation of 6.7% (Woodman et al., 2001).

Cutaneous microvascular function: Participants were positioned supine on a bed whilst instrumentation took place to allow haemodynamic variables and skin blood flow to form a stable baseline. LDF probes (Perimed, AB, Järfälla, Stockholm, Sweden) were fixed with adhesive tape to the volar aspect of the forearm and anteromedial aspect of the calf. Participants were instrumented with a rapid BP cuff inflator (Hokanson E20/AG101 Rapid Cuff Inflation System, D. E. Hokanson, Inc., Bellevue, Washington, USA) on the proximal arm and thigh. At both sites, rapid inflator cuffs were proximal to the LDF recording sites. Cutaneous microvascular function was assessed in the arm and leg at different time points, simultaneously to the FMD measurements outlined above. Firstly, the arm was measured, after a period of baseline stabilisation, a one-minute baseline measurement was performed before a five-minute period of vascular occlusion by inflating the cuff to 220 mmHg. During this period, known as the skin microvascular *biological zero*, non-zero flux recordings were to be expected due to the Brownian motion of red blood cells within the microfluidic compartment. At the end of the five-minute occlusion, the cuff was rapidly deflated, and the resulting hyperemic response was recorded for 3 minutes. The above process was repeated afterwards on the leg, as described above. Continuous beat-by-beat BP was obtained from a digit during the post-occlusive reactive hyperaemia (PORH) protocol (Finapres, Amsterdam, Netherlands).

Skin microvascular flux was collected and quantified in arbitrary units (PU) by the LDF probes. Flux measurements were collected (PowerLab 4/25, ADInstruments Ltd., Oxford, UK) and stored for analyses (LabChart v8.1.8, ADInstruments Ltd.). For PORH protocols, skin

microvascular flux data was extracted in 1 second averages for offline analysis in line with previous studies (Stupin et al., 2018). The absolute peak response of PORH was defined as the highest one second average value to occur after cuff release within a 180 second window. Area under the curve calculations were performed to estimate total skin blood flow in a given time period. A baseline area-under-the-curve was calculated using a rolling integral function of second-average flux values for the 180 s period prior to cuff inflation. A 3-minute (5-minute for leg) PORH peak response area-under-curve value (*AUC PORH*) was also calculated as a rolling integral function of second-average values from the time of cuff release for 180 seconds (300 seconds for leg). *AUC PORH* was adjusted for baseline AUC by subtracting baseline AUC from *AUC PORH* to give *AUC adj*. The percentage difference between baseline and PORH peak was also calculated (*%base-peak*). Cutaneous microvascular blood flow was indexed as cutaneous vascular conductance (CVC, $\text{CVC} = \text{flux}/\text{MAP}$, $\text{PU} \cdot \text{mmHg}^{-1}$) in order to account for any potential effects of changes in BP on skin blood flow.

Cerebrovascular measurements:

CBF (MCA blood velocity): Following 15 minutes of rest in a supine position, bilateral middle cerebral artery velocity (MCAv) was continuously measured through the temporal window using TCD. Two 2-MHz Doppler probes (Spencer Technologies, Seattle, USA) were adjusted until an optimal signal was identified (Willie et al., 2011) and held in place using a Marc 600 head frame (Spencer Technologies, Seattle, USA). Participants were instrumented with a two-way valve mouthpiece (Hans Rudolph, Oxford, UK) from which partial pressure of end tidal CO₂ (P_{ETCO_2}) was measured using a calibrated gas analyser (ML206 ADInstruments, Colorado Springs, USA). Continuous beat-by-beat BP was obtained from a digit (Finapres, Amsterdam,

Netherlands). All data was sampled at 50 Hz with the data acquisition system PowerLab via the interface LabChart 8 (ADInstruments, Colorado Springs, USA).

Cerebrovascular reactivity: Cerebrovascular reactivity (CVR) to carbon dioxide (CO₂) was assessed whilst lying in a supine position. Participants were connected to a prefilled Douglas bag via a two-way valve mouthpiece (Hans Rudolph, Oxford, UK) prior to a one-minute resting baseline measurement (MCAv, MAP and P_{ET}CO₂) where they breathed normal atmospheric air at a normal breathing rate. Following the baseline measurement, participants were then switched, via the Douglas bag, to inhaling a 5% CO₂ (21% O₂, 5% CO₂, N₂ balance) gas mixture for three minutes. Participants were instructed to breathe at their normal breathing rate. MCAv, MAP and P_{ET}CO₂ baseline values were averaged over one minute of supine rest. Subsequently MCAv, MAP and P_{ET}CO₂ were collected as one second averages throughout the three-minute rebreathing period. The peak response was taken as a rolling 30 second average (Koep et al., 2022). CVR was calculated both in absolute and relative (%) change from baseline MCAv per unit increase in P_{ET}CO₂ (mmHg) as the gain of the linear relationship between CBFv and P_{ET}CO₂ using the equations:

- Absolute CVR_{CO₂} = $\Delta\text{MCAv} / \Delta\text{PETCO}_2$
- Relative CVR_{CO₂} = $\% \text{MCAv change from baseline} / \Delta\text{PETCO}_2$

Where Δ is the change from baseline to the 30 second rolling average peak of MCAv. To correct for any changes in MAP during CO₂ inhalation, cerebrovascular conductance was calculated (CBFv/MAP) and the absolute and relative (%) gains for CVR_{CO₂MAP} vs. PETCO₂ were also calculated.

Cerebral autoregulation: Ten minutes following CVR, dCA was assessed using a squat-to-stand procedure that induced transient changes in arterial BP (Smirl et al., 2015, Claassen et al., 2009a). Participants began replicating the experimenter whilst performing the manoeuvres, which involved moving from an upright standing position to a squat position where the legs achieved an approximate 90° angle. Participants performed one set of squat-to-stand manoeuvres at 0.10Hz (5 second held stand – 5 second held squat) while breathing normal atmospheric air. The manoeuvres were preceded by 5 minutes of seated rest and participants were told to keep their eyes open and avoid strenuous breathing patterns if possible. Squat-to-stand manoeuvres were performed at 0.10Hz to create physiologically relevant changes in BP that present challenges to the autoregulatory system that are typically experienced in daily life (Simpson and Claassen, 2018). The BP-MCAv relationship during these manoeuvres were analysed in accordance with the most recent guidelines (Claassen et al., 2016) using TFA. Data from the five-minute recording of squat-to-stand manoeuvres were extracted from LabChart beat-to-beat using BP tracing. TFA was applied using Ensemble (version 1.0.0.28, Elucimed, Wellington, NZ) to calculate associated power (gain), timing (phases) and linearity (coherence) at the point estimate of the driven frequency (0.10 Hz) (Claassen et al., 2016). Where gain (absolute) represents the dampening effect of CA on the magnitude of BP oscillations, normalised gain is also provided to reflect the relative changes in CBFv to a given change in (%/mmHg) (Claassen et al., 2016). The threshold used for the minimum value of coherence was based on pre-defined TFA settings (0.4). The 0.10Hz forced oscillations employed for this protocol fall within the low frequency (LF) domain (0.07-0.2Hz), as such LF results were reported (Zhang et al., 1998).

5.2.4. Statistical Analysis

Analysis was performed using Statistical Package for Social Sciences (SPSS) [Version 29; SPSS Inc., Chicago, IL]. Visual inspection of histograms and the Shapiro-Wilk test was employed to assess the normality of the data (Mishra et al., 2019). Baseline characteristics between conditions were analysed using an independent samples *t*-test or the Mann-Whitney test if the data was non-parametric. All FMD% data were analysed, and are presented, as covariate-controlled for baseline artery diameter measured prior to the introduction of hyperaemia in each test; this approach is more accurate for scaling changes in artery diameter than simple percentage change (Atkinson et al., 2013, Atkinson and Batterham, 2013). Statistical significance was delimited at $P < 0.05$. Data are presented in text as mean (95% confidence intervals) unless otherwise stated and exact *P* values are cited; *P* values of '0.000' provided by the statistics package are reported as <0.001).

5.3. Results

Seven females with rheumatoid arthritis and eight female control participants were recruited. Participants were well matched for age ($P = 0.56$) and BMI ($P = 0.91$). There were no significant differences between groups for anthropometry and basic health data at baseline (Table 1).

Table 5.1. Baseline participant characteristics (mean $\pm$ SD).

	RA (n=7)	Control (n=8)	<i>P</i> value
Age (years)	54 $\pm$ 11	51 $\pm$ 9	0.56
Height (cm)	164 $\pm$ 5	161 $\pm$ 5	0.20
Weight (kg)	76 $\pm$ 22	74 $\pm$ 12	0.82
BMI (kg/m ²)	29 $\pm$ 9	29 $\pm$ 5	0.91
SBP (mmHg)	142 $\pm$ 21	131 $\pm$ 10	0.21
DBP (mmHg)	67 $\pm$ 11	73 $\pm$ 4	0.27
MAP (mmHg)	105 $\pm$ 11	102 $\pm$ 5	0.55
Medication (n of participants)			
DMARDS	7	/	/
Hypertension medication	2	2	/

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure.

5.3.1. Microvasculature

Baseline CVC in the arm: There was no difference in baseline CVC in the RA group compared to their non-RA counterparts (-0.05 PU.mmHg⁻¹, 95% CI = -0.19, 0.09, $P = 0.42$).

CVC PORH in the arm: Peak CVC in the RA group was lower than in the control group, though this did not reach statistical significance (-0.37 PU.mmHg⁻¹, 95% CI = -0.82, 0.08, $P = 0.10$).

There was no difference in time to peak (2 sec, 95% CI = -8, 4, $P = 0.70$), AUC PORH (-20

PU.mmHg⁻¹, 95% CI = -71, 31, $P = 0.50$), AUC adj (-11 PU.mmHg⁻¹, 95% CI = -41, 18, $P = 0.50$) or %base-peak (21%, 95% CI = -281, 324, $P = 0.50$) in the RA group compared to their non-RA counterparts.

Baseline CVC in the leg: There was no difference in baseline CVC in the RA group compared to their non-RA counterparts (-0.03 PU.mmHg⁻¹, 95% CI = -0.05, 0.11, $P = 0.42$).

CVC PORH in the leg: The %base-peak in the RA group was lower than in the control group, though this did not reach statistical significance (-94%, 95% CI = -202, 15, $P = 0.08$). There was no difference in peak (0.02 PU.mmHg⁻¹, 95% CI = -0.43, 0.46, $P = 0.94$) time to peak (0 sec, 95% CI = -9, 9, $P = 0.96$), AUC PORH (3 PU.mmHg⁻¹, 95% CI = -41, 46, $P = 0.89$) or AUC adj (-3 PU.mmHg⁻¹, 95% CI = -33, 27, $P = 0.84$) in the RA group compared to their non-RA counterparts.

Table 5.2. CVC PORH in the arm and leg (mean $\pm$ SD).

	RA	Control	<i>P</i> value
Arm	(<i>n</i> = 4)	(<i>n</i> = 8)	
Baseline (PU.mmHg-1)	0.16 $\pm$ 0.09	0.21 $\pm$ 0.10	0.42
Peak (PU.mmHg-1)	0.82 $\pm$ 0.20	1.19 $\pm$ 0.37	0.10
Time to peak(sec)	16 $\pm$ 3	14 $\pm$ 9	0.70
AUC PORH*	68 $\pm$ 24	88 $\pm$ 42	0.50
AUC adj*	39 $\pm$ 9	50 $\pm$ 25	0.50
%base-peak*	519 $\pm$ 334	498 $\pm$ 150	0.50
Leg	(<i>n</i> = 3)	(<i>n</i> = 8)	
Baseline (PU.mmHg-1)	0.17 $\pm$ 0.04	0.14 $\pm$ 0.06	0.42
Peak (PU.mmHg-1)	0.83 $\pm$ 0.15	0.81 $\pm$ 0.32	0.94
Time to peak (sec)	16 $\pm$ 2	16 $\pm$ 6	0.96
AUC PORH	69 $\pm$ 16	66 $\pm$ 31	0.89
AUC adj	37 $\pm$ 9	40 $\pm$ 22	0.84

%base-peak	381 ± 34	474 ± 90	0.08
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**Non-parametric data*

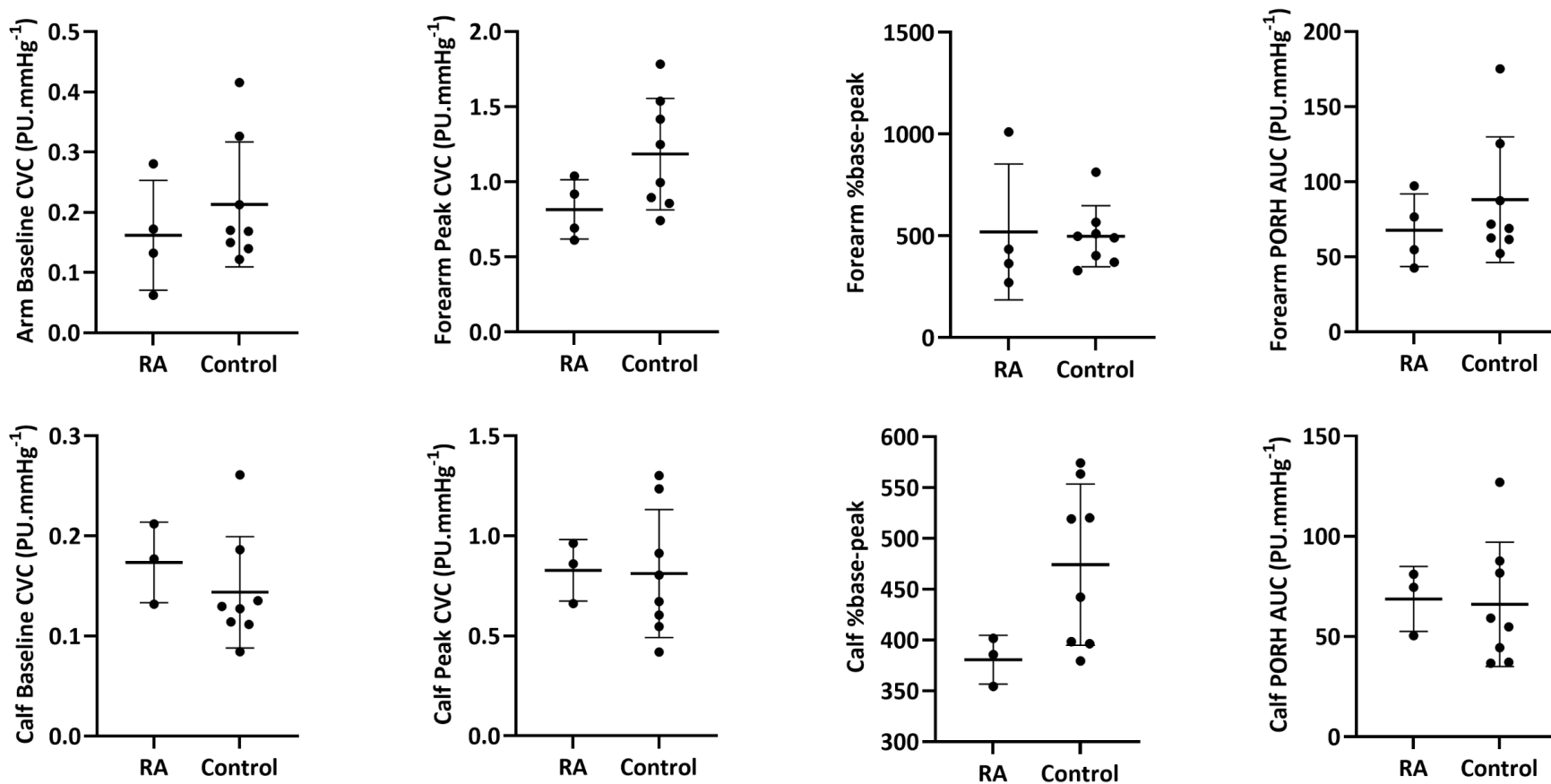


Figure 5.1. Baseline CVC, peak CVC, %base-peak and PORH AUC in the forearm (top) in $n = 4$ people living with RA and $n = 8$ non-RA controls, and in the calf (bottom) in $n = 3$ people living with RA and $n = 8$ non-RA controls.

5.3.2. Macrovasculature

Brachial artery flow mediated dilation: There was no difference in FMD% in the RA group compared to their non-RA counterparts (-0.2%, 95% CI = -1.98, 1.54, $P = 0.77$), nor in allometrically scaled FMD% (-0.2%, 95% CI = -1.9, 1.5, $P = 0.78$). There was no difference in baseline diameter (-0.002 cm, 95% CI = -0.050, 0.045, $P = 0.91$), peak diameter (-0.003 cm, 95% CI = -0.054, 0.048, $P = 0.90$), time to peak (4 sec, 95% CI = -20, 28, $P = 0.71$) or shear AUC (10.23×10^3 , 95% CI = -7.26, 27.73, $P = 0.23$) in the RA group compared with their non-RA counterparts.

Femoral artery flow mediated dilation: FMD% in the RA group was lower than in their non-RA counterparts, but this did not reach statistical significance (-1.4%, 95% CI = -3.4, 0.6, $P = 0.14$), similarly, allometrically scaled FMD% was lower in the RA group than the control group but was also non-significant (-1.5%, 95% CI = -3.2, 0.3, $P = 0.09$). Time to peak in the RA group was greater than in their non-RA counterparts, but did not reach statistical significance (24 sec, 95% CI = -13, 62, $P = 0.18$). There was no difference in baseline diameter (-0.010 cm, 95% CI = -0.103, 0.083, $P = 0.82$), peak diameter (-0.019 cm, 95% CI = -0.113, 0.074, $P = 0.66$) or shear AUC (-1.4×10^3 , 95% CI = -7.8, 5.0, $P = 0.64$) in the RA group compared to their non-RA counterparts.

Table 5.3. Brachial artery and femoral artery flow mediated dilation (mean $\pm$ SD).

	RA (n= 7)	Control (n= 8)	P value
Brachial			
Baseline diameter (cm)	0.36 $\pm$ 0.05	0.36 $\pm$ 0.04	0.91
Peak diameter (cm)	0.39 $\pm$ 0.05	0.39 $\pm$ 0.04	0.90
FMD%*	6.5 $\pm$ 1.5	6.7 $\pm$ 1.6	0.77
Allometrically scaled FMD%	6.5 $\pm$ 1.6	6.7 $\pm$ 1.4	0.78
Time to peak (sec)	54 $\pm$ 17	50 $\pm$ 24	0.71
Shear AUC (10 ³)	29.9 $\pm$ 17.5	19.7 $\pm$ 13.9	0.23
Femoral			
	(n= 6)	(n= 7)	
Baseline diameter (cm)	0.58 $\pm$ 0.10	0.59 $\pm$ 0.05	0.82
Peak diameter (cm)	0.61 $\pm$ 0.10	0.63 $\pm$ 0.05	0.66
FMD%	5.2 $\pm$ 1.5	6.6 $\pm$ 1.7	0.14
Allometrically scaled FMD%	5.0 $\pm$ 1.5	6.7 $\pm$ 1.3	0.09
Time to peak (sec)	69 $\pm$ 39	45 $\pm$ 21	0.18
Shear AUC (10 ³)	12.0 $\pm$ 0.5	13.4 $\pm$ 0.5	0.64

*Non- parametric data

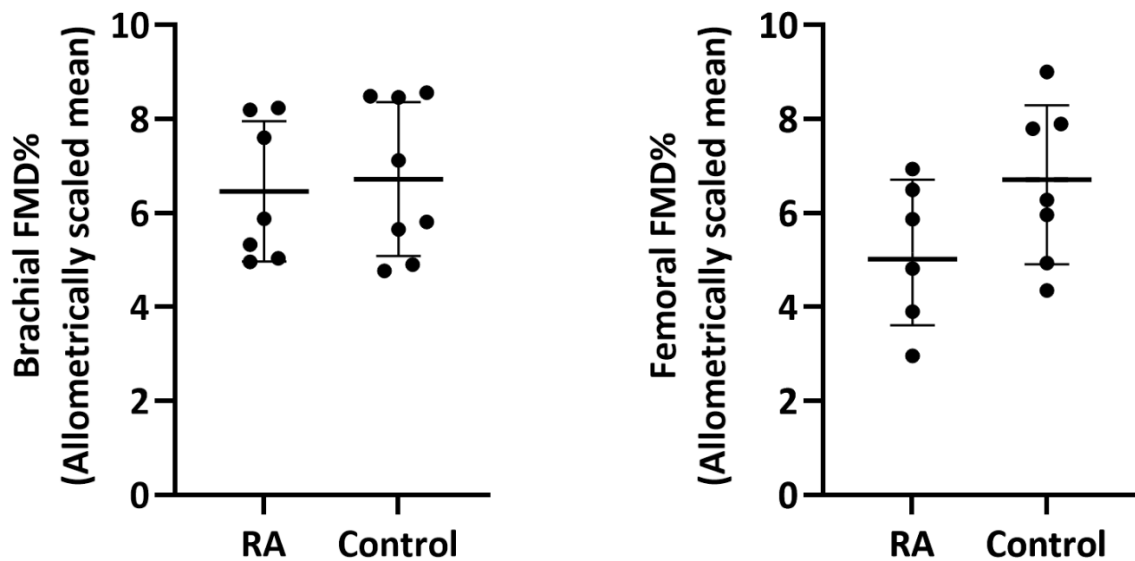


Figure 5.2. Flow-mediated dilation (FMD) in the brachial artery (left) in $n = 7$ people living with RA and $n = 8$ non-RA controls, and in the femoral artery (right) in $n = 6$ people living with RA and $n = 6$ non-RA controls. Mean line denotes the allometrically scaled mean values.

5.3.3. Cerebrovasculature

Baseline haemodynamics: MCAv, PETCO₂, respiratory rate, MAP and resting heart rate were not different between groups ($P > 0.05$, Table 4).

Table 5.4. Baseline haemodynamics (mean $\pm$ SD).

	Rheumatoid Arthritis ($n=5$)	Control ($n=4$)	P value
MCAv (cm.s)	69.3 $\pm$ 26.9	61.0 $\pm$ 9.8	0.59
PETCO ₂ (mmHg)	40.6 $\pm$ 1.0	37.4 $\pm$ 4.2	0.23
Respiratory rate (BPM) *	14 $\pm$ 4	14 $\pm$ 5	0.88
MAP (mmHg)	101 $\pm$ 20	105 $\pm$ 14	0.73
Resting HR (beats.min ⁻¹)	67 $\pm$ 11	62 $\pm$ 3	0.48

Acronyms: MCAv; Middle cerebral artery velocity, PETCO₂; Partial pressure of end tidal carbon dioxide, MAP; mean arterial pressure. *Mann Whitney test employed.

CO₂ reactivity data (30 second peak): There were no differences between resting CBVC and CBVR. There were also no differences in the absolute or relative gain of CVR_{CO_2} and CVR_{CO_2MAP} (accounting for the effects of MAP changes on CVR_{CO_2}) during CO₂ inhalation between the RA and control groups ($P > 0.05$, Table 5)

Table 5.5. Baseline and CO₂ reactivity data from the 30 second rolling average peak (mean $\pm$ SD).

	Rheumatoid Arthritis (<i>n</i> =4)	Control (<i>n</i> =4)	<i>P</i> value
Resting			
CBVC (cm.s ⁻¹ /mmHg ⁻¹)*	0.73 $\pm$ 0.42	0.59 $\pm$ 0.12	0.77
CVBR (mmHg ⁻¹ /cm.s ⁻¹)	1.66 $\pm$ 0.72	1.75 $\pm$ 0.30	0.82
CO₂ Reactivity Test			
Absolute CVR_{CO_2} (cm.s/mmHg ⁻¹)	3.4 $\pm$ 1.5	2.5 $\pm$ 1.2	0.40
Relative CVR_{CO_2} (%cm.s/mmHg ⁻¹)	5.0 $\pm$ 1.3	4.0 $\pm$ 1.5	0.35
Absolute CVR_{CO_2MAP} (cm.s.mmHg ⁻¹ . mmHg ⁻¹)*	0.03 $\pm$ 0.02	0.02 $\pm$ 0.01	0.48
Relative CVR_{CO_2MAP} (%cm.s/mmHg ⁻¹ . mmHg ⁻¹)	3.5 $\pm$ 0.9	2.9 $\pm$ 1.3	0.53

Acronyms: CBVC; cerebrovascular conductance, CBVR; cerebrovascular resistance.

Cerebral autoregulation: Normalised gain was lower in the RA group than in their non-RA counterparts, though this did not reach statistical significance (-0.29 %cm.s⁻¹.%mmHg⁻¹, 95% CI = -0.58, 0.00, $P = 0.05$), similarly, gain was also lower in the RA group than the control group, but was also non-significant (-0.17 cm.s⁻¹. mmHg⁻¹, 95% CI = -0.45, 0.11, $P = 0.19$). MCAv power was lower in the RA group than in the control though, though this did not reach statistical

significance (-116 cm/s^2 , 95% CI = $-300, 67$, $P = 0.11$). Coherence, phase, gain and BP power were not different between the RA and control groups. ($P > 0.05$, Table 6).

Table 5.6. Transfer function analysis parameters from dynamic cerebral autoregulation using squat-stand manoeuvres (0.1Hz) (mean $\pm$ SD).

	Rheumatoid Arthritis ($n=5$)	Control ($n=4$)	<i>P</i> value
Coherence	0.75 ± 0.12	0.84 ± 0.13	0.35
Phase (radians)	0.29 ± 0.17	0.36 ± 0.10	0.49
Gain ($\text{cm.s}^{-1} \cdot \text{mmHg}^{-1}$)	0.58 ± 0.19	0.75 ± 0.14	0.19
Normalised Gain ($\% \text{cm.s}^{-1} \cdot \% \text{mmHg}^{-1}$)	0.95 ± 0.20	1.24 ± 0.16	0.05
BP power ($\text{mmHg}^2 \text{s}^{-2}$)	579 ± 246	661 ± 443	0.73
MCAv power (cm/s^2)	193 ± 63	309 ± 123	0.11

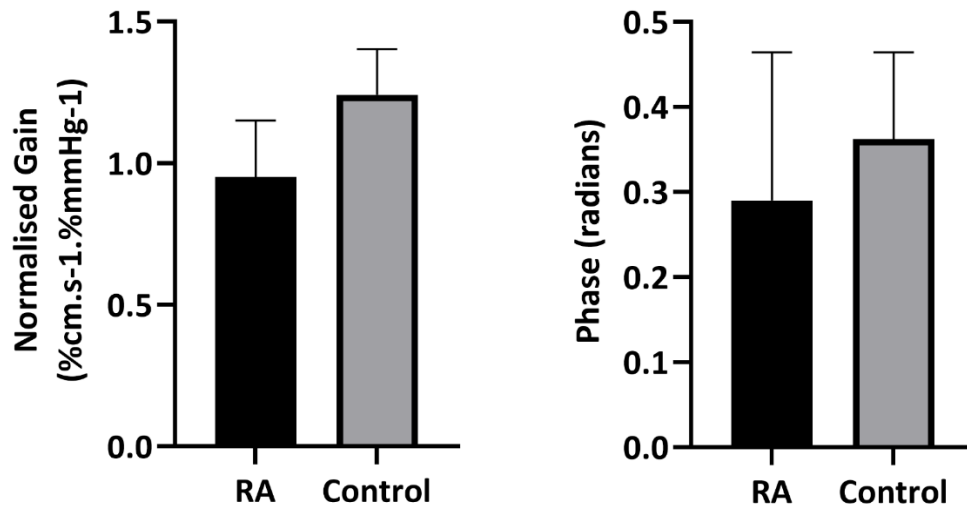


Figure 5.3. Normalised gain ($\% \text{cm.s}^{-1} \cdot \% \text{mmHg}^{-1}$) [left] and phase (radians) [right] in $n = 5$ people living with RA and $n = 4$ non-RA controls.

5.4. Discussion

The aim of this study was to examine the impact of RA on micro-, macro- and cerebrovascular function and compare this to non-RA, matched controls via the concurrent assessment of vascular function throughout the vasculature tree. It is important to note that no significant differences were found between groups and that all results are suggestive of possible trends in the data that need to be further explored. The present study demonstrated that in the microvasculature, peak PORH response was reduced in the forearm in the RA group when compared to the control group, meanwhile the percentage change from baseline to peak was lower in the leg in the RA group – both of which may indicate reduced microvasculature function. Meanwhile, the study also suggests RA may cause vascular dysfunction in the macrovasculature of the lower limbs, whilst macrovascular function in the upper limbs is preserved. In the cerebrovasculature, the RA group displayed higher baseline CBFv and lower normalised gain, during the squat-to-stand procedure, compared to the control group, whereas there were no differences in cerebrovascular reactivity between groups. Meanwhile, the small sample size in the present study limits making definitive conclusions from these data, it highlights a clear need for further research to interrogate the effect of RA on the vasculature and whether there is a cascading effect between the different vascular beds – which would present an opportunity to detect cardiovascular dysfunction as early as possible.

5.4.1. Microvasculature

This study confirms previous findings that RA patients exhibit microvascular dysfunction, though most previous research has utilised endothelial peripheral artery tonometry (Endo-PAT) which measures microvascular function from the fingers (Bordy et al., 2018) different mechanisms of control of the microcirculation, compared to the forearm, and to LDF as

employed in the present study (Roustit and Cracowski, 2012). Though, the present study is in agreement with Arosio et al. (2007) who also demonstrated that forearm microvascular peak flow after a period of ischemia was lower in people living with RA than in healthy controls using LDF. In addition to confirming previous reports that microvasculature function is impaired in RA (Bordy et al., 2018), which could be a driver for the development of CVD as it predicts and precedes the development of conduit artery atherosclerosis in the general population (Gutterman et al., 2016), this study extends the finding to a lesser studied vascular bed in RA. Previously proposed potential reasons for the attenuated peak response in the arm are the lack of release and action of prostaglandins (Engelke et al., 1996) and neurogenic mechanisms (Arosio et al., 2007) which may reduce the ability of the microvasculature to vasodilate. Though, it is evident that further research should be conducted to enhance understanding of the mechanisms behind reduced microvascular (dys)function in RA.

In the leg, there was less evidence for impaired microvascular function although %base-peak was lower in the RA group in comparison to the control group. It is not possible to ascertain why the peak CVC response to hyperaemia was numerically reduced only in the forearm site and not the calf in RA, when compared with the control group in the present study. However, this finding is in agreement with previous research which demonstrated that the forearm skin area seems to be more susceptible than the leg skin area to alterations in SkBF in response to pathological processes or ageing (Smith et al., 2013). A denser network of skin capillaries in the ventral forearm in comparison with the lateral calf (Pasyk et al., 1989) may contribute to the greater sensitivity of the forearm to exhibit changes in SkBF and microvascular function, compared with the calf. Moreover, due to poor signal strength we were only able to obtain

accurate measurements of calf SkBF in three of the RA group, which reduces statistical power of the comparisons between groups for this specific site.

5.4.2. Macrovasculature

The present study identified that FMD was diminished in the lower limbs in RA in comparison to the control group, though this did not reach statistical significance. In contrast, FMD in the upper limbs was similar between RA and the control group. There is evidence to suggest that the attenuation of FMD in the lower limbs of RA patients may be due to their higher susceptibility to develop atherosclerosis. During post-mortems of 28 elderly people, Vink et al. (2002) found that atherosclerosis and intimal thickening were more common in coronary and lower limb arteries (e.g., iliac and femoral arteries) than in the brachial artery, thus, suggesting that the lower limbs may be more vulnerable to vascular dysfunction. In addition, lower limb vascular function has also been shown to be impaired in patients with peripheral artery disease (PAD), whilst upper limb vascular function was preserved (Sanada et al., 2005). Sanada et al. (2005) went on to suggest that the impairment of vascular reactivity in the lower limbs may occur before that of the upper limbs, postulating the potential for different rates of progression of atherosclerosis in the different extremities.

Comparable lower limb vascular function studies are scarce in people living with RA so it is difficult to ascertain why RA may cause impairments in leg vascular function. A pilot study assessing lower limb vascular characteristics in RA observed no differences between the clinical group and age- and sex-matched controls (Tehan et al., 2019). However, another study by (Amin et al., 2014) observed higher prevalence of abnormal ankle-brachial pressure index (ABPI) suggesting possible higher incidence of subclinical atherosclerosis in people living with RA. There are a myriad of potential explanations for the potentially diminished lower limb

vascular function in people living with RA in the present study such as the effects of systemic inflammation, physical inactivity and the presence of other traditional CVD risk factors. Overall, it is conceivable that the systemic inflammation evident in RA may cause vascular dysfunction to occur in the lower limbs before the upper limbs as has been suggested in non-RA populations (Vink et al., 2002)

Alongside previous research, the findings of this study may indicate that assessment of vascular function in the lower limbs may be a better early indicator of CVD than in upper limb vascular function. This is an important finding for RA, as most research in the population to date focuses on the assessment of upper limb vascular function, which is equivocal, some report reduced FMD% in RA compared to non-RA populations (Xu et al., 2017, Fan et al., 2012, Di Minno et al., 2015), whilst others report no statistical differences (Van Doornum et al., 2003). Whereas the findings of this study suggest it may be more advantageous for future research to assess vascular function in the lower limbs to detect signs of CVD as early as possible.

5.4.3. Cerebrovasculature

When assessing the cerebrovasculature, this study identified that people with RA had higher baseline CBFv than the control group. There are multiple potential explanations for this finding, firstly people with RA could have enhanced CBF. However, there is no way to unequivocally prove this as at present we are only able to measure CBFv as an index of CBF as TCD does not provide feedback regarding vessel diameter (Willie et al., 2011, Ainslie and Hoiland, 2014), which importantly can affect measurement accuracy of CBF with TCD (de Heus et al., 2018). CBFv is only an adequate surrogate of absolute flow if the insonated vessel diameter remains constant (Ainslie and Hoiland, 2014), but diameter changes, though unlikely during rest

(Serrador et al., 2000) cannot be ruled out. Another explanation could be that the increased CBFv in the RA group is secondary to a stenotic process within the cerebrovasculature. Endothelial dysfunction is largely suspected to play a role in increased CVD risk in RA (England et al., 2018) and there is emerging evidence that reveals RA may be associated with a higher risk of cerebrovascular diseases, including an increased risk of stroke with an odds ratio of 1.73-2.12 compared to the general population (Wiseman et al., 2016). Moreover, animal studies have reported that arthritis resulted in endothelial dysfunction of the MCA, possibly via the upregulation of the arginase pathway, thus reducing NO production (Bordy et al., 2020). This evidence, alongside the knowledge that CBFv would increase because of the narrowing of a vessel due to increased peripheral vascular resistance that may occur as a result of endothelial dysfunction (DeLong and Sharma, 2019), offers another potential explanation for the higher baseline CBFv in the RA group. It should also be noted that the RA group had a slightly higher baseline PETCO₂ value than the control group, as such it would be expected that CBF would be higher in the RA group given that higher PaCO₂ results in cerebral arteriolar vasodilation (Ainslie and Duffin, 2009). Future research would benefit from a larger sample size to further investigate potential differences in CBF between people living with RA and non-RA counterparts.

There were no differences between groups for cerebrovascular reactivity to CO₂. This is a somewhat unexpected finding given that there is evidence people with RA may have a higher risk of endothelial dysfunction and cerebrovascular disease (Wiseman et al., 2016). However, it is important to note that the mechanistic pathways responsible for the role of CO₂ in regulating cerebrovascular tone are not fully identified, thus any impairment may represent dysfunction from a number of mechanistic pathways. NO is believed to play a major role in the

chemoregulation of CBF, with animal studies showing that NO participates in cerebral CO₂-dependent vasomotor reactivity. Human studies have also shown NO is critical in chemoregulation of CBF, but whether this is via neural or endothelial mediated pathways in humans remains unknown (Lavi et al., 2003, Garry et al., 2015). There are also currently no reference values for what would be deemed efficient CVR, as such it could be that both the RA and control groups within this study could have normal/poor CVR. Traditionally higher CVR has been related to greater aerobic fitness (Bailey et al., 2013), whilst lower CVR has been related to aging (Miller et al., 2019, Bakker et al., 2004) and conditions such as stroke (Markus and Cullinane, 2001). However, findings are equivocal and contrasting research has shown a negative relationship between CVR and fitness (Thomas et al., 2013, Furby et al., 2020). This is largely attributed to differences in methodology when measuring CVR which makes comparisons of findings challenging. As such CVR in people living with RA should be investigated further in a larger sample, especially given the high CVD risk in the population and evidence that impaired CVR can be related to brain conditions such as dementia (SS Meel-van den Abeelen et al., 2014) and stroke (Markus and Cullinane, 2001)

Interestingly, dCA appeared to demonstrate a more efficient response in the RA group compared with the control group in the present study. A lower normalised gain in the RA groups indicates a reduced magnitude of changes in BP on CBF oscillations, suggesting that the RA group were better able to buffer BP oscillations. There is no comparable research assessing dCA within people with RA and given the low sample size and statistical power of the present study it is difficult to draw firm conclusions at this stage. There is evidence from other populations that have also demonstrated unexpected findings, including the attenuation of dCA in young fit women compared to men (Labrecque et al., 2019). Additionally, previous

research has shown that CVD risk factors were not associated with a reduction in dCA when age was considered, suggesting that despite vascular maladaptation's that are associated with CVD risk factors, the ability of the cerebral blood vessels to maintain stable CBF upon changes in BP is preserved (Maxwell et al., 2022). This relationship should be further investigated in RA specific novel CVD risk factors such as systemic inflammation.

At present there is insufficient data to establish reference and normative values for TFA parameters (Panerai et al., 2023). Gain, in particular, is highly variable and no clear criteria for abnormal values are currently available (Intharakham et al., 2019). The most recent guidance suggests that due to no defined thresholds being recommended, caution should be applied to interpreting reduced values of dCA as impaired autoregulation (Panerai et al., 2023). Therefore, it is difficult to assess any potential increase in dCA in people living with RA. The mechanisms behind the autoregulation response are still an area of debate with unexplained signals and unknown mechanisms likely at play (Koller and Toth, 2012), thus it is likely that autoregulation is not a fully endothelial mediated response and other vascular responses could remain intact preserving the autoregulation response. As such it is important that future research should be conducted to create clinically relevant parameters (Panerai et al., 2023) and enhance understanding of the underlying mechanisms of autoregulation, which is especially potent in people with RA given the emerging evidence of associated cerebrovascular disease (Wiseman et al., 2016).

5.4.3. The impact of rheumatoid arthritis of vascular function and the role of physical activity and exercise

The impact of RA on vascular function is related to both the prevalence of traditional cardiovascular risk factors (e.g., physical inactivity, hypertension, hypercholesterolemia,

diabetes, smoking) (Baghdadi et al., 2015) and the direct effects of RA systemic inflammation on the vasculature (Skeoch and Bruce, 2015, Alkaabi et al., 2003b, Bordy et al., 2018). Both traditional and RA specific CVD risk factors can lead to changes in vascular structure and function that may contribute to the development of atherosclerosis (Skeoch and Bruce, 2015). One of the most important non-pharmacological interventions to prevent vascular function and CVD is PA, due to its ability to reverse endothelial dysfunction, as well as producing anti-atherogenic and anti-inflammatory effects (Metsios et al., 2010). Significant positive adaptations in endothelial function in both the micro- and macro- vasculature have been shown after three and six months when completing an exercise intervention combining aerobic and resistance exercise (Metsios et al., 2014). Thus, suggesting that physical activity and exercise may play an important role in reducing the effect of both traditional and RA specific CVD risk factors.

5.4.4. Limitations

The major limitation of the present study is the low sample size and thus statistical power. Although the study can postulate about the findings, definitive conclusions cannot be made due to the lack of power. It must also be acknowledged that TCD assesses blood velocity rather than blood flow and relies on assumptions that the diameter of the MCA did not change during cerebrovascular measures (CO_2 reactivity and cerebral autoregulation). Research evidence does suggest that MCAv is a reliable index of CBF if the intonated vessel maintains a constant diameter. MCA diameter has been shown to be consistent during modest changes in CO_2 (+5 mmHg) (Ainslie and Hoiland, 2014) as employed in this study. Another limitation of the present study is the absence of ultrasound scans of the internal carotid artery (ICA) which would allow for better representation of flow response and dilation of cranial vessels. Another limitation

of this study is that not all traditional and novel RA CVD risk factors were assessed which may contribute to variability in the present data. Particularly cardiorespiratory fitness and PA levels were not assessed, these measures would have provided further context to any differences observed in outcome measures.

A final limitation was loss of data during data collection procedures. In the assessment of the microvasculature, three participants from the RA group had insufficient arm LDF data and four participants from the RA group had insufficient leg LDF data, both due to poor signals. In the assessment of the microvasculature one femoral FMD from the RA group and another from the control group were not of a sufficient image quality to be analysed. In the assessment of CVR four participants in the RA group and four participants in the control group a signal deemed sufficient to run the measurement was unobtainable. In the cerebral autoregulation assessment one further participant in the RA group was unable to produce BP oscillations sufficient to run transfer function analysis. This data loss, in part, led to difficulty making strong conclusions around outcome measures.

5.4.5. Conclusion

This study has provided preliminary data to suggest that people living with RA may exhibit vascular dysfunction in both the micro- and macrovasculature, whilst the cerebrovascular appears unaltered, though no findings were statistically significant. Future research should focus on further investigation of the cerebrovasculature in this population so that CVD risk can be fully understood, and care pathways developed to help patients manage these risks.

**CHAPTER 6: POOR REPORTING OF EXERCISE
INTERVENTIONS FOR PEOPLE WITH
RHEUMATOID ARTHRITIS MAY AFFECT
IMPLEMENTATION: A SYSTEMATIC
SCOPING REVIEW**

6.1. Introduction

RA is a chronic auto-immune inflammatory disease, characterised by swelling and inflammation of the joints, pain, fatigue, neuropsychiatric disorders (e.g., depression, anxiety and cognitive dysfunction) and systemic manifestations (e.g., cardiovascular and lung diseases, osteoporosis and bone fracture, etc) (Hammam et al., 2019). The abovementioned symptoms and manifestations negatively impact health-related quality of life (HRQoL) in RA (Pollard et al., 2005, Matcham et al., 2014).

An ever growing and important behavioural intervention that could have a positive impact on a multitude of RA symptoms is regular exercise. Studies investigating the effects of regular exercise in people living with RA have shown improvements in functional capacity (Baillet et al., 2011), aerobic capacity (Van Den Ende et al., 2000), muscle strength (Baillet et al., 2011, Van Den Ende et al., 2000), fatigue (Rongen-van Dartel et al., 2015), mental wellbeing (Kelley and Kelley, 2014), sleep (Durcan et al., 2014) and in cardiovascular health (Lee et al., 2012b, Summers et al., 2019). Meanwhile, no studies have reported any adverse effects from people living with RA engaging in exercise of varied intensity and types (Metsios and Lemmey, 2015). However, despite these well-documented benefits, people living with RA do not usually engage with exercise (Manning et al., 2012, O'Dwyer et al., 2014) and their overall PA levels are low compared with the general population (Lee et al., 2012b, Summers et al., 2019). It is therefore important to summarise the characteristics of existing exercise interventions in people living with RA to gain a representation of how the issue of physical inactivity in RA has been tackled to date, as this is a key area that could be improved in the management of RA.

Amongst the barriers for exercise in people living with RA, a lack of support, adequate advice (Veldhuijzen van Zanten et al., 2015a) and confidence in prescribing exercise to people with

RA from rheumatology healthcare professionals (HCPs) (Law et al., 2013, McKenna et al., 2019) may negatively impact how well exercise is prescribed and adhered to. There is a distinct lack of information and guidance available to HCPs on how to incorporate PA and/or exercise into the clinical management of RA (Metsios and Kitas, 2018), which is likely a major factor in the insecurity to prescribe exercise. This lack of provision is somewhat surprising as embedding PA into healthcare systems is a target of the World Health Organization (World Health Organisation, 2020). The absence of improvement in this area is concerning, a potential cause is poor reliability and validity in research conducted to date on exercise interventions in people living with RA. Recent data has shown that descriptions of exercise interventions in different clinical disciplines are often lacking in detail for replication and thus difficult to validate (Slade and Keating, 2012, Hoffmann et al., 2013) – meaning confidence to include them in prescription may be diminished. Poor reporting can lead to clinicians struggling to deliver effective exercise protocols, as their ability to interpret study findings is altered by the level of reporting (Glasziou et al., 2008).

To our knowledge, no previous study has investigated the level of reporting of exercise interventions in studies with people living with RA. Previous reviews have examined areas such as mechanisms, effectiveness and implementation of PA and exercise in people living with RA (Metsios and Kitas, 2018) and exercise dose in clinical trials in people living with RA (Boniface et al., 2020). Meanwhile, this review has utilised the Consensus to Exercise Reporting Template (CERT) (Slade et al., 2016) was specifically developed to improve reporting for exercise interventions; and it also creates a framework to assess the level of reporting of existing exercise interventions. CERT comprises of 16 items listed under 7 sections (what, who, how, where, when, how much, tailoring and how well) and is used as a checklist to ensure that the

minimum key items considered essential to report replicable exercise interventions are present (Slade et al., 2016). CERT is a particularly useful tool to assess exercise reporting in people living with RA given the barriers to becoming physically active within the population it is extremely important that reporting is of a high quality. A systematic scoping review approach was chosen to inspect exercise interventions in the RA population and examine how they are reported. Therefore, the aims of this systematic scoping review were to; (i) summarise the existing exercise interventions utilised in randomised controlled trials (RCTs) involving individuals living with RA and; (ii) assess the level of reporting of exercise interventions in RCTs for individuals with RA by applying the CERT criteria.

6.2. Methods

6.2.1. Registration

This systematic scoping review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018) and is registered in the OSF Registries database (doi: doi.org/10.17605/OSF.IO/T8QN4).

6.2.2. Search Strategy and Study Selection

Searches were performed on five databases (PubMed, Web of Science, Embase, Cochrane Library and Scopus) by entering key words related to the population and intervention (Supplementary File 1). Searches were limited to peer-reviewed articles written in English, published from the inception of each database through to January 2023.

For inclusion, studies were required to fulfil the following criteria: i) randomised controlled trials (RCTs) with an experimental condition that included an exercise intervention in adults ($\geq$

18 years) with a diagnosis of RA; ii) interventions should have lasted ≥ 2 weeks; studies included supervised and unsupervised exercise; iii) studies written in English. Studies were excluded if they were review studies, observational studies, sub-studies, acute exercise studies, isolated protocol papers, behavioural intervention studies (with no structured exercise), and hand only exercise interventions. Also excluded were multicomponent interventions where exercise was a minor component; physiotherapy interventions (e.g. joint manipulation, kinesio tape); not involving RA patients (at least 50% of the population should have been diagnosed with RA); abstracts and conference proceedings.

On completion of the searches, members of the study team (D.B. and J.J.) independently selected the studies to be included based on the title, abstract and full text of each potential manuscript. Discrepancies were identified and solved through discussion with a third author (T.P.)

6.2.3. Data Extraction

Two members of the study team (D.B. and J.J.) independently extracted study data using a purpose-developed data extraction sheet, after which a mutual consensus was reached. Discrepancies were identified and solved through discussion. The following characteristics were extracted from each selected study: author(data), study design, participant information, characteristics of the intervention.

6.2.4. Application of the CERT

Two members of the study team (D.B. and J.J.) independently scored each included study by applying CERT (Slade et al., 2016). Both reviewers applied CERT to all selected studies and any discrepancies in scoring were identified and solved through discussion. The CERT includes 16

categories encompassing 19 separate items considered essential in the reporting of reproducible exercise interventions listed under seven distinct domains: what (materials), who (provider), how (delivery), where (location), when and how much (dosage), tailoring (what and how) and how well (compliance / planned and actual) (Slade et al., 2016). A more detailed description of the CERT items is available in the Explanation and Elaboration statement (Supplementary File 2) (Slade et al., 2016). The statement was used by reviewers to guide the scoring of each item. Each item was rated as a 'yes' (criteria met, clearly reported) or a 'no' (item not reported or not clearly described). The number of items rated 'yes' were summed to provide an overall score ranging from 0 to 19, with 19 being all CERT items clearly described. If studies specifically referenced published protocols, supplementary files or online appendices, the reviewers retrieved these and extracted any additional data, where relevant.

6.2.5. Data Analysis

A narrative synthesis was performed to describe the data from the included studies. Studies were described in the text and tables and were organised by key details, such as population (i.e., sex/gender, age and disease activity), intervention type, comparison and adverse events. In addition, we reported data on the exercise interventions which included; type of exercise, frequency (sessions/week), duration (min/session), intensity, supervision, setting, monitoring and additional support resources.

6.3. Results

6.3.1. Literature Search

The search of the databases identified a total of 3872 studies (Figure 1). Following the removal of duplicates ($n=1733$), 2139 studies were screened for inclusion. Of these, 2035 were excluded after reviewing the title and abstract. The remaining 104 papers were selected for

full reading, whereby 60 were excluded for being conference abstracts ($n= 18$), not RCT's ($n= 11$), sub-studies of previously included studies ($n= 10$), not involving structured exercise interventions ($n= 10$), trial registrations ($n= 2$), short communications ($n= 2$), a book chapter ($n= 1$), utilising exercise as a minor component ($n= 1$), a physiotherapy intervention ($n= 1$), utilising hand only exercise ($n= 1$), a letter to the editor ($n= 1$), an undetected duplicate ($n= 1$), and finally, an exercise intervention less than two weeks long ($n= 1$). Therefore 44 were included in the review and are listed in the qualitative analysis.

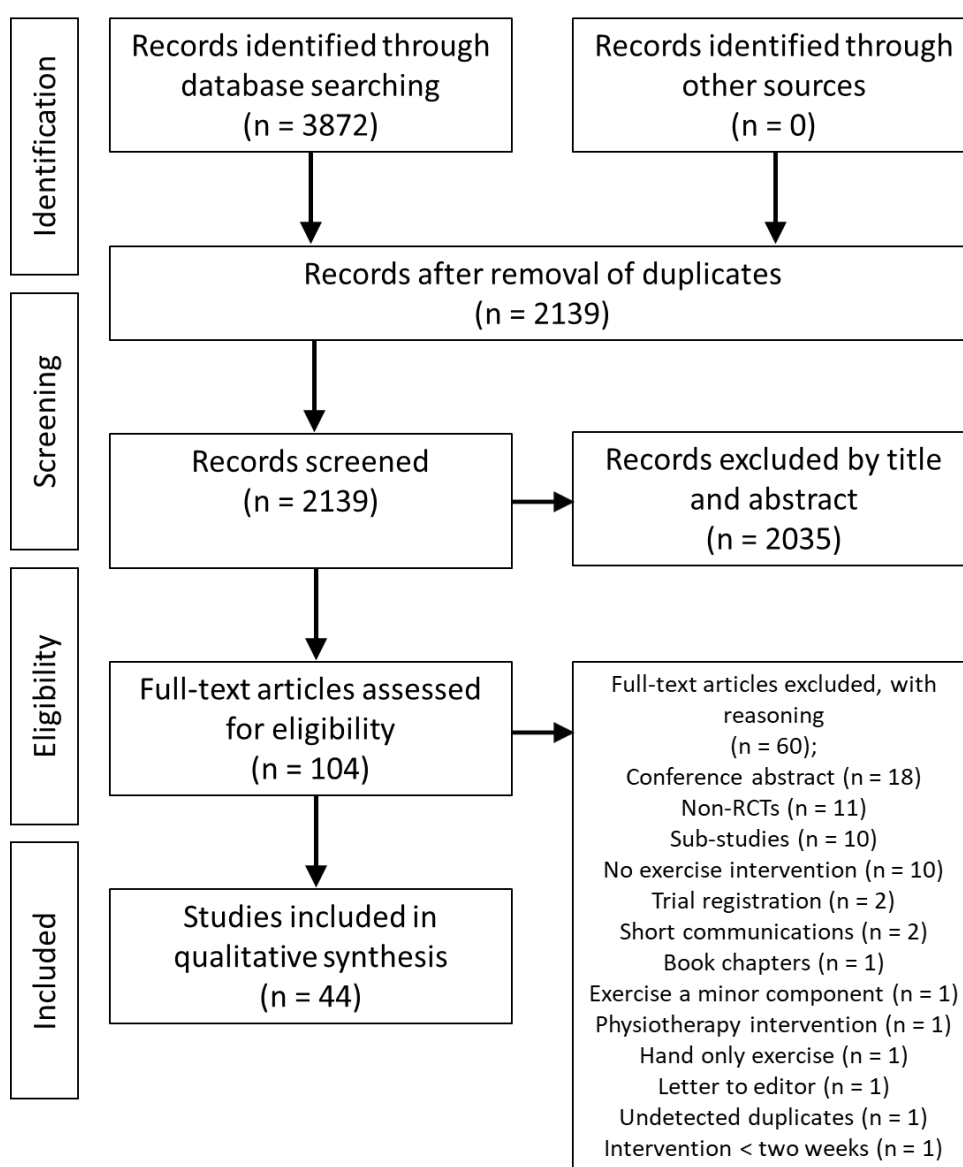


Figure 6.1. Flow-chart of the systematic review.

6.3.2. Study and Participant Characteristics

Three thousand two hundred and twenty-nine people participated in the studies [Females ($n=2568$, Males ($n=561$) and undefined ($n=100$)], with most studies being conducted with young to middle-aged adults (~25 to 59 years old), with six studies being conducted in older adults (>60 years old). Half (22) of studies reported disease activity (DAS-28) with an average of 3.64. Eight studies reported disease activity levels that would be classified as low/in remission (≤ 3.2). Meanwhile, 13 studies reported mean disease activity levels that would be classified as moderate activity (3.2-5.1) and only one study involved participants with high mean disease activity (>5.1).

Table 6.1. Characteristics of the manuscripts.

Author (date)	Population				Intervention type	Comparison	Adverse events
	<i>n</i>	Gender	Age	Disease activity (DAS28, DAS28-crp, DAS28-esr)			
Azeez et al. (2020)	66	♀ ♂	58.5 (34-73) 63 (36-74) ^	2.37 (0.49-3.7) 2.69 (0.49-5.3) ^	Combined exercise (AE, DRE)	Usual care + PA/Ex advice/education	NR
Lange et al. (2019)	74	♀ ♂	70±2	2.37±1.00	Combined exercise (AE, DRE, RoM, balance) + education	RoM and functional exercise + education	Yes*
Manning et al. (2014)	108	♀ ♂	55±15	4.78±1.54 ‡	Upper extremity DRE + education and self- management	Usual care	NR
Rodrigues et al. (2020)	48	♀	59±6	2.71±0.87	Arm 1. High-load DRE exercise Arm 2. Low-load DRE exercise + blood flow restriction	Non-exercise control	Yes: exercise induced pain/discomfort (n=15)
Gautam et al. (2019)	72	♀ ♂	44±2	5.04±0.16	Yoga	Usual care	NR
Siqueira et al. (2017)	133	♀	54±6	3.90±1.11	Arm 1. Water-based AE Arm 2. Land-based AE	Non-exercise control	Yes: AEv; pain, joint swelling, stiffness, cold,

Author (date)		Population			Intervention type	Comparison	Adverse events
							hypertension (n=16) SAEv: stroke/death (n=2)
Pukšić et al. (2021)	57	♀ ♂	55±11	2.54±0.85	Yoga	RA advice/education	Yes: vertigo (n=1)
Strasser et al. (2011)	40	♀ ♂	57±9	3.57±1.10 ¥	Combined exercise (AE, DRE)	RoM	NR
Ganesan et al. (2020)	166	♀ ♂	42±8	4.86±0.68	Yoga	Usual care	NR
Garcia-Morales et al. (2020)	144	♀	49±12	2.47±0.92	Arm 1. Combined exercise (AE, DRE, sport) + Mediterranean Diet	Non-exercise control	NR
					Arm 2. Combined exercise (AE, DRE, sport)		
					Arm 3. Mediterranean Diet		
McKenna et al. (2021)	20	♀	58±7	NR	Walking	PA/Ex advice/education	Yes*
Shapoorabadi et al. (2016)	36	♀	52±8	NR	AE	Usual care	NR
Baxter et al. (2016)	33	♀ ♂	62±12	NR	Walking	Nutritional advice/education	None

Author (date)	Population				Intervention type	Comparison	Adverse events
Durcan et al. (2014)	80	♀ ♂	60±10	NR	Combined exercise (DRE, RoM, walking)	PA/Ex advice/education	NR
Piva et al. (2019)	59	♀ ♂	59±10	4.00±1.21	DRE	Neuromuscular electrical stimulation	None
Rezaei et al. (2020)	56	♀	41±7	NR	Walking	Usual care	NR
van Rensburg et al. (2012)	46	♀	47±8	3.27±0.91	Combined exercise (AE, DRE)	Non-exercise control	NR
Hall et al. (1996)	139	♀ ♂	58±11	NR	Arm 1. Combined exercise (DRE, RoM) (hydrotherapy) Arm 2. Combined exercise (DRE, RoM) (land)	Non-exercise control	NR
Lourenzi et al. (2017)	60	♀ ♂	52±4	4.20±1.08	DRE	Non-exercise control	None
Seneca et al. (2015)	51	♀ ♂	61(27-79) 54(23-71) ^	2.77(0.96-4.12), 1.80(0.97,4.37) ^	Combined exercise (AE, DRE)	Recommended self- administered exercise	NR
Baillet et al. (2009)	50	♀ ♂	54±11	4.45±1.56	Combined exercise (AE, DRE, balance)	RA advice/education	None
Bilberg et al. (2005)	47	♀ ♂	49(32-62) 46(21-65) ^	4.05±1.4	Combined exercise (AE, DRE)	Usual care	NR
Breedland et al. (2011)	34	♀ ♂	48±11	2.99±1.02	Combined exercise (AE, DRE, sport) + education	Non-exercise control	NR

Author (date)	Population				Intervention type	Comparison	Adverse events
Neuberger et al. (2007)	310	♀ ♂	55.5(40-70) ^	NR	<i>Arm 1.</i> Combined exercise (Low impact AE, DRE) (group class) <i>Arm 2.</i> Combined exercise (Low impact AE, DRE) (home)	Non-exercise control	NR
van den Berg et al. (2006)	160	♀ ♂	49.65±13.4	NR	Combined exercise (AE, DRE, RoM)	PA/Ex advice/education	NR
Jahanbin et al. (2014)	66	♀	49±10	NR	Combined exercise (AE, DRE, IRE)	Non-exercise control	NR
De Jong et al. (2003)	309	♀ ♂	53.5(18) 54.0(26) ^	NR	Combined exercise (AE, DRE, sport)	Non-exercise control	NR
McMeeken et al. (1999)	36	♀ ♂	51±13	NR	DRE	Non-exercise control	NR
Daltroy et al. (1995)	37 (71 incl. non- RA)	♀ ♂	39±2	6.30±0.61	AE	Non-exercise control	NR
Bearne et al. (2002)	108	♀ ♂	NR	NR	Combined exercise (IRE, functional/balance exercise)	Non-exercise control	NR
van den Ende et al. (1996)	100	♀ ♂	52±12	NR	<i>Arm 1.</i> Combined exercise (high intensity) (AE, DRE)	PA/Ex advice/education	NR

Author (date)		Population			Intervention type	Comparison	Adverse events
					Arm 2. Combined exercise (low intensity) (RoM, IRE) Arm 3. Combined exercise (low intensity, individualised) (RoM, IRE)		
Häkkinen et al. (2001)	70	♀ ♂	49±11	4.65±1.1	DRE + encouraged AE	RoM	NR
Loeppenthin et al. (2022)	38	♀ ♂	56±10	2.13±0.55	AE	Usual care	None
Allam et al. (2018)	30	♀ ♂	42±9	NR	Combined exercise (AE, walking, arm exercise) + hot application and TENS	Relaxation	NR
Lemmey et al. (2019)	28	♀ ♂	58±10	3.29±1.18	DRE	RoM	None
Ward et al. (2018)	26	♀ ♂	55±10	NR	Yoga	Usual care	Yes: Musculoskeletal pain/nausea (n=11)
Somers et al. (2020)	50	♀ ♂	56±11	NR	Combined exercise (AE, IRE) + lifestyle behavioural weight management education	Usual care	NR
Komatireddy et al. (1997)	49	♀ ♂	59±10	NR	DRE	Non-exercise control	NR
Stenström et al. (1996)	54	♀ ♂	54(45-64) 55(48-64) ^	NR	Combined exercise (DRE, walking, RoM)	Relaxation	NR
Flint-Wagner et al. (2009)	24	♀ ♂	51±13	NR	Combined exercise (AE, DRE)	Usual care	NR

Author (date)	Population				Intervention type	Comparison	Adverse events
Westby et al. (2000)	30	♀	56±10	NR	Combined exercise (AE, DRE, RoM) + education	Usual care	NR
Lyngberg et al. (1994)	24	♀ ♂	67±9	NR	Combined exercise (AE, DRE)	Non-exercise control	NR
Ambrosino et al. (2020)	40	♀ ♂	27±5	3.63±0.48	Exergaming	Non-exercise control	NR
Häkkinen et al. (1999)	65	♀ ♂	49±10	NR	DRE	RoM	NR

Age and disease activity is expressed as weighted mean±SD unless otherwise stated; ^ expressed as median (interquartile range); † expressed as mean (95% CI). Acronyms: AE; aerobic exercise, DRE; dynamic resistance exercise, IRE; isometric resistance exercise, S; sports activities, TENS; transcutaneous electrical nerve stimulation NR; not reported, RoM; range of motion exercises, AEv; adverse events, SAEv; Serious adverse event.

**No specific information given. #data provided by authors on request.*

6.3.3. Intervention Characteristics

Interventions lasted an average of 18 weeks (range 4-104 weeks). In total, there were 50 distinct exercise interventions employed across 44 studies, with one study employing three exercise intervention arms (Van den Ende et al., 1996) and three studies employing two exercise intervention arms (Hall et al., 1996, Neuberger et al., 2007, Siqueira et al., 2017, Rodrigues et al., 2020).

Types of exercise

Just over half of interventions (27/50) employed a combined exercise intervention. There were 12 different combinations of exercise intervention, with aerobic exercise (AE) combined with dynamic resistance exercise (DRE) ($n=10$) and AE combined with DRE and sport ($n=3$) being the most employed. In the 23 interventions which employed a single mode of exercise, the interventions utilised were DRE ($n=10$), AE ($n=5$), yoga ($n=4$), walking ($n=3$) and exergaming ($n=1$).

Frequency of exercise per week

Frequency of exercise sessions per week was reported for 48/50 interventions, with 41 reporting a set number of sessions per week and seven reporting a range (e.g., 2-3 sessions per week). The frequency of sessions per week ranged from 0.5 (once fortnightly) to 7. The average number of sessions per week was 2.8. Where interventions reported a range, the median across those interventions was 3 sessions per week.

Exercise duration

Exercise session duration was reported for 41/50 interventions, with 27 reporting a set duration and 14 reporting a time range (e.g., 30-60 mins). The duration of sessions ranged from

12-120 mins. The average duration of sessions was 57 mins. Where interventions reported a range the median across those interventions was 40 mins per session.

Intensity of exercise

There were 74 distinct exercise intensities employed within the 50 exercise interventions. 38 exercise intensities were clearly defined by authors providing the relevant information (e.g., 60-80% HR_{max}). Eight exercise intensities were reported by authors without specific parameters (e.g., “moderate intensity”) and in 25 interventions the authors only provided detail on the mode of exercise and exercise intensities were then derived from the Compendium of Physical Activities (Ainsworth et al., 2011). Further to this, no information could be gathered to identify three exercise intensities, so they were defined as not reported. The most employed exercise intensity was moderate ($n= 32$), followed by high intensity ($n= 11$) and low intensity ($n= 8$). Where exercise intensity was reported as a range, the most common was moderate-to-high intensity ($n= 13$), followed by low-to-high intensity ($n= 5$) and low-to-moderate intensity ($n= 2$).

Exercise supervision

The presence of exercise supervision was reported in 43/50 interventions. Twenty-six reported supervised exercise, while 12 studies reported that exercise was unsupervised and six reported partly supervised exercise.

Exercise monitoring

Exercise monitoring was reported in 29/50 exercise interventions. The most employed monitoring technique was the use of exercise logs/diaries ($n= 14$), followed by in-person monitoring ($n= 10$), HR monitoring ($n= 8$) and RPE monitoring ($n=5$). Power output, phone calls

and exercise recall were all utilised in two studies each, while pain during exercise, repetitions and pedometers were utilised in one study each. Twenty-one interventions did not report monitoring.

Additional support resources

Additional support resources were present in 19/50 interventions. In total there were 32 additional support resources reported, with studies using between one and four additional support resources. The most used resources were familiarisation sessions ($n=6$) and videotapes of exercise/exercise guides ($n=6$). Further resources that were used include education session/s ($n=5$), motivational support programmes/strategies ($n=4$) and music ($n=2$). The following were each utilised once: *Wii Fit* system, yoga CD, phone calls, HR monitor, email, access to website, occupational therapy, walking routes map and physiotherapy sessions.

Table 6.2. Characteristics of exercise interventions.

Study	Type of exercise	Frequency (sessions/w)	Duration (min/session)	Intensity	Supervision	Setting	Monitoring	Additional support resources
Azeez et al. (2020)	Combined exercise (AE, DRE)	NR	NR	AE: LI-HI** DRE: MI**	NS	Home	- Exercise log/diary	-Physiotherapist sessions
Lange et al. (2019)	Combined exercise (AE, DRE, RoM, balance)	3-7	62	AE: HI (70-89% HRmax) DRE: LI-HI (40-80% 1RM)	PS	Gym and home	NR	NR
Manning et al. (2014)	Upper extremity DRE	7	NR	HI (RPE 13-17)	PS	Home and in-person component€	- In-person monitoring - Exercise log/diary - RPE	- Educational session - Motivational strategy (BCTs)
Rodrigues et al. (2020) [High Load RT]	DRE	2	NR	MI (50-70% 1RM)	S	Intrahospital gym	- In-person monitoring	NR
Rodrigues et al. (2020) [Low Load RT + BFR]	DRE-BFR	2	NR	LI (20-30% 1RM)	S	Intrahospital gym	- In-person monitoring	NR
Gautam et al. (2019)	Yoga	5	120	LI**	S	Laboratory	NR	NR
Siqueira et al. (2017) [Hydrotherapy]	AE	3	20-35	LI-HI (4-8 Borg CR-10)	S	Temperate pool	- In-person monitoring - RPE	- Familiarisation session - Motivational support programme

Study	Type of exercise	Frequency (sessions/w)	Duration (min/session)	Intensity	Supervision	Setting	Monitoring	Additional support resources
Siqueira et al. (2017) [Land-based]	AE	3	20-35	LI-HI (4-8 Borg CR-10)	S	Poolside	- In-person monitoring - RPE	- Familiarisation session - Motivational support programme
Pukšić et al. (2021)	Yoga	2	90	LI**	S	Departmental gym	- In-person monitoring	NR
Strasser et al. (2011)	Combined exercise (AE, DRE)	2	NR	AE: MI (60% VO ₂ max) DRE: HI (70% 1RM)	S	NR	- HR	NR
Ganesan et al. (2020)	Yoga	3	30	LI**	S	Yoga centre and home	- Phone calls	NR
Garcia-Morales et al. (2020)¥	Combined exercise (AE, DRE, sport)	2	80-90	AE: MI-HI (65-85% HRmax) DRE: MI** Sport: MI**	S	NR	NR	NR
McKenna et al. (2021)	Walking	2-5	30-50	MI (50-80% HRR/12-17 RPE)	PS	Outdoor	- In-person monitoring - Exercise log/diary	NR
Shapoorabadi et al. (2016)	AE	3	12-35	MI (60-70% HRR)	S	NR	NR	- Familiarisation session
Baxter et al. (2016)	Walking	3-4	NR	MI (6 out of 10 RPE)	NS	Outdoor	- Exercise log/diary	- Familiarisation session

Study	Type of exercise	Frequency (sessions/w)	Duration (min/session)	Intensity	Supervision	Setting	Monitoring - Pedometer	Additional support resources - Walking routes map
Durcan et al. (2014)	Combined exercise (DRE, RoM, walking)	5	30-60	DRE: MI (50% 1RM) Walking: LI- MI*	NS	Home	NR	NR
Piva et al. (2019)	DRE	2-3	45	LI-HI (40-80% 1RM)	NR	NR	NR	NR
Rezaei et al. (2020)	Walking	3-5	35-50	MI*	PS	Sports hall and Outdoor	- In-person monitoring	- Familiarisation session
van Rensburg et al. (2012)	Combined exercise (AE, DRE)	2-3	45	AE: MI-HI (60-80% HRmax) DRE: MI**	S	NR	NR	NR
Hall et al. (1996) [Hydrotherapy]	Combined exercise (DRE, RoM) (hydrotherapy)	2	30	DRE: MI**	NR	Hospital hydrotherap y pool	NR	NR
Hall et al. (1996) [Land Exercise]	Combined exercise (DRE, RoM) (land)	2	30	DRE: MI**	NR	Hospital gym	NR	NR
Lourenzi et al. (2017)	DRE	2	50-60	MI (50-70% 1RM)	S	NR	NR	NR
Seneca et al. (2015)	Combined exercise (AE, DRE)	2	60	AE: HI (15-16 RPE)	PS	NR	NR	NR

Study	Type of exercise	Frequency (sessions/w)	Duration (min/session)	Intensity	Supervision	Setting	Monitoring	Additional support resources
				DRE: HI (12 RM)				
Baillet et al. (2009)	Combined exercise (AE, DRE, balance [gym and hydrotherapy])	5	105	AE: MI-HI (60-80% HRmax)	S	Gym and hydrotherapy pool	- Exercise log/diary	- Occupational therapy programme
Bilberg et al. (2005)	Combined exercise (AE and DRE)	2	45	DRE: MI** AE: MI*	S	Temperate pool	NR	NR
				DRE: MI** AE: MI (60% HRmax)				
Breedland et al. (2011)	Combined exercise (AE [land/water], DRE, sport)	2	90	DRE: LI-MI (40-60% 1RM)	S	Outpatient rehabilitation centre	NR	- Education sessions
				Sport/Aqua jogging: MI-HI**				
Neuberger et al. (2007) [Class exercise]	Combined exercise (AE, DRE)	3	60	AE: MI-HI (60-80% HRmax)	S	Fitness centre	- HR - Exercise recall	NR
				DRE: MI**				
Neuberger et al. (2007) [Home exercise]	Combined exercise (AE, DRE)	3	60	AE: MI-HI (60-80% HRmax)	NS	Home	- HR - Exercise recall	- Videotape of exercises

Study	Type of exercise	Frequency (sessions/w)	Duration (min/session)	Intensity	Supervision	Setting	Monitoring	Additional support resources
van den Berg et al. (2006)	Combined exercise (AE, DRE, RoM)	5	13-43	DRE: MI** AE: MI-HI (60-80% HRmax)	NS	Home	NR	- Education sessions - Access to website - Email
Jahanbin et al. (2014)	Combined exercise (AE, DRE, IRE)	2	45	DRE: MI** NR	NR	NR	NR	NR
De Jong et al. (2003)	Combined exercise (AE, DRE, sport)	1 (fortnightly)	75	AE: MI-HI (70-90% HRmax) DRE: HI* Sport: MI-HI**	S	NR	- HR - RPE	NR
McMeeken et al. (1999)	DRE	2	45	MI**	NR	NR	NR	NR
Daltroy et al. (1995)	AE	3	30	MI-HI (60-80% HRmax)	NS	Home	- Exercise log/diary - Phone calls	- HR monitor
Bearne et al. (2002)	Combined exercise (IRE, functional/balance exercise)	2	30-45	IRE: MI**	S	Hospital	NR	NR
van den Ende et al. (1996) [High Intensity]	Combined exercise (AE, DRE)	3	60	AE: HI (70-85% HRmax)	S	NR	NR	NR

Study	Type of exercise	Frequency (sessions/w)	Duration (min/session)	Intensity	Supervision	Setting	Monitoring	Additional support resources
				DRE: HI*				
van den Ende et al. (1996) [Low Intensity]	Combined exercise (IRE, RoM)	2	60	IRE: LI*	S	NR	NR	NR
van den Ende et al. (1996) [Low Intensity Individualised]	Combined exercise (IRE, RoM) [individualised]	2	NR	IRE: LI*	S	NR	NR	NR
Häkkinen et al. (2001)	DRE + encouraged AE	2	45	DRE: MI (50-70% 1RM)	NR	NR	- Exercise log/diary	NR
Loeppenthin et al. (2022)	AE	3	20-30	MI-HI (40-80% watt max)	S	NR	- Power output (Watts) - HR	NR
Allam et al. (2018)	Combined exercise (AE, walking, arm exercise)	3	30	AE: MI (70% HRmax) Walking: MI**	NR	NR	NR	NR
Lemmey et al. (2019)	DRE	2	NR	HI (80% 1RM)	S	Community gym	- Exercise log/diary	NR
Ward et al. (2018)	Yoga	4	95	LI**	S	Exercise room	- In-person monitoring	- Yoga CD
Somers et al. (2020)	Combined exercise (AE, IRE)	3	35-50	AE: MI-HI (55%-70% HRR)	S	Fitness centre	- In-person monitoring - HR - RPE	- Education sessions

Study	Type of exercise	Frequency (sessions/w)	Duration (min/session)	Intensity	Supervision	Setting	Monitoring	Additional support resources
IRE: NR								
Komatireddy et al. (1997)	DRE	2-3	20-27	MI (3/4 out of 10 RPE)	NS	Home	- Exercise log/diary	- Videotape of exercises - Exercise guide
Stenström et al. (1996)	Combined exercise (DRE, walking, RoM)	5	30	DRE: MI** Walking: MI**	NS	Home	-Exercise log/diary	- Videotape of exercises - Exercise guide - Music - Phone calls
AE: NR								
Flint-Wagner et al. (2009)	Combined exercise (AE, DRE)	3	75	DRE: HI (70-85% 1RM)	S	NR	- Exercise log/diary	- Familiarisation sessions - Motivational support programme
Westby et al. (2000)	Combined exercise (AE, DRE, RoM)	3	45-60	AE: MI (60-75% HRmax)	NS	Home	- Exercise log/diary - HR	- Education sessions - Exercise guide - Music
DRE: LI* AE: MI-HI (50-70% max pulse increment)								
Lyngberg et al. (1994)	Combined exercise (AE, DRE)	2	45		NS	NR	- HR - Power output - Pain - Reps	NR
DRE: MI**								
Ambrosino et al. (2020)	Exergaming	NR	NR	HI**	NS	Home	- Exercise log/diary	- Wii Fit system
Häkkinen et al. (1999)	DRE	2	45	MI (50-70% 1RM)	NS	Home	- Exercise log/diary	NR

Acronyms: LI; low intensity, MI; moderate intensity, HI; high intensity, AE; aerobic exercise, DRE; dynamic resistance exercise, IRE; isometric resistance exercise, S; sports activities, RoM; Range of motion exercise, BFR; blood flow restriction, NS; not supervised, PS; partly supervised, S;

*supervised and NR; not reported. Exercise intensity; *as reported by the authors; ** based in The 2011 Compendium of Physical Activities (Ainsworth et al., 2011), whenever an activity was described without additional information (e.g., walking), we classified intensity based on the most popular/standard way of performing such activity (e.g., walking classified as moderate intensity). ¥; this exercise intervention was performed in both exercise groups in the study, €; no extra information given on setting. [...] denotes the specific intervention when more than one exercise intervention was employed in a study.*

6.3.4. Consensus on Exercise Reporting Template

The CERT evaluation of the reporting of exercise interventions of the 44 included studies is shown in Table 3. In total there were 50 exercise interventions employed across the 44 studies. The median score was seven (range 1-13) out of a possible score of 19. Thirteen exercise interventions had a CERT score of ≥ 10 , while the remaining 37 interventions (74%) all scored < 10 . This indicates that the majority of the exercise intervention details were missing from studies. Five CERT items were clearly described by at least 50% of the studies (Figure 2). These included descriptions of instructor qualifications ($n = 36$ studies), whether exercise was completed individually or in a group ($n = 32$ studies), if exercise supervised or unsupervised ($n = 39$ studies), the setting of the exercise ($n = 26$ studies) and whether exercise was generic or individually tailored ($n = 36$ studies). The following items were poorly reported across most studies: how adherence to exercise is measured and reported ($n = 5$ studies), description of motivation strategies ($n = 4$ studies), how intervention fidelity was assessed ($n = 6$ studies), and if the intervention was delivered as planned ($n = 5$ studies).

Table 6.3. Consensus to Exercise Reporting Template (CERT) scoring.

Study	1.	2.	3.	4.	5.	6.	7a.	7b.	8.	9.	10.	11.	12.	13.	14a.	14b.	15.	16a.	16b.	Total number of items fulfilling criteria
Azeez et al., (2020)	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Lange et al., (2019)	0	1	1	1	0	0	0	1	0	1	1	0	1	1	1	0	0	0	1	10
Manning et al., (2014)	1	1	1	1	0	1	0	0	0	1	1	0	0	0	1	0	0	1	0	9
Rodrigues et al., (2020) (High Load RT)	0	1	0	1	0	0	1	1	0	0	0	1	1	1	1	1	1	0	1	11
Rodrigues et al., (2020) (Low Load RT + BFR)	0	1	0	1	0	0	0	1	0	0	1	1	1	1	1	1	1	0	1	11
Gautam et al., (2019)	0	1	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	4
Siqueira et al., (2017) (Hydrotherapy)	1	1	0	1	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0	10
Siqueira et al., (2017)	1	1	1	1	0	0	0	1	1	0	1	1	1	1	1	0	0	0	0	11

Study	1.	2.	3.	4.	5.	6.	7a.	7b.	8.	9.	10.	11.	12.	13.	14a.	14b.	15.	16a.	16b.	Total number of items fulfilling criteria
(Land-based)																				
Pukšić et al., (2021)	0	1	1	1	0	0	0	1	0	1	1	1	1	0	0	0	0	0	0	8
Strasser et al., (2011)	0	1	0	1	0	0	1	1	1	0	0	0	0	1	1	1	1	0	1	10
Ganesan et al., (2020)	0	1	0	1	0	0	0	0	1	1	0	0	1	1	1	0	0	0	0	7
Garcia-Morales et al., (2020) (DEP+MD)	1	1	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	5
Garcia-Morales et al., (2020) (DEP)	1	1	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	5
McKenna et al., (2021)	0	1	1	1	1	0	0	1	1	1	0	1	1	1	1	1	0	1	0	13
Shapoorabadi et al., (2016)	1	1	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	5
Baxter et al., (2016)	1	0	1	1	1	0	0	0	1	1	0	1	0	0	0	0	1	0	1	9
Durcan et al., (2014)	0	1	1	1	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	9

Study	1.	2.	3.	4.	5.	6.	7a.	7b.	8.	9.	10.	11.	12.	13.	14a.	14b.	15.	16a.	16b.	Total number of items fulfilling criteria
Piva et al., (2019)	0	1	0	0	1	0	1	1	0	0	0	1	0	1	1	1	1	0	0	9
Rezaei et al., (2020)	0	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	3
van Rensburg et al., (2012)	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	3
Hall et al., (1996) (Hydrotherapy)	0	1	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	0	0	5
Hall et al., (1996) (Land Exercise)	0	1	1	0	0	0	1	0	0	0	0	0	1	0	1	0	0	0	0	5
Lourenzi et al., (2017)	1	1	0	1	0	0	0	0	1	0	0	1	0	1	1	1	1	0	0	9
Seneca et al., (2015)	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	5
Baillet et al., (2009)	0	1	0	1	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	6
Bilberg et al., (2005)	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3
Breedland et al., (2011)	1	1	1	1	0	1	0	1	0	1	1	0	1	1	1	1	1	0	0	13

Study	1.	2.	3.	4.	5.	6.	7a.	7b.	8.	9.	10.	11.	12.	13.	14a.	14b.	15.	16a.	16b.	Total number of items fulfilling criteria
Neuberger et al., (2007) (Class exercise)	0	0	1	1	0	0	1	1	0	0	0	0	1	0	1	1	0	0	0	7
Neuberger et al., (2007) (Home exercise)	0	0	1	1	0	0	1	1	0	1	0	0	1	0	1	1	0	0	0	8
van den Berg et al., (2006)	1	1	1	1	0	0	1	1	0	1	1	0	1	0	1	1	0	0	0	11
Jahanbin et al., (2014)	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
De Jong et al., (2003)	0	0	1	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	5
McMeeken et al., (1999)	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	5
Daltroy et al., (1995)	1	1	1	1	0	0	0	0	1	1	0	0	1	1	1	1	0	0	0	10
Bearne et al., (2002)	1	1	1	1	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	7
van den Ende et al., (1996) (High Intensity)	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	4

Study	1.	2.	3.	4.	5.	6.	7a.	7b.	8.	9.	10.	11.	12.	13.	14a.	14b.	15.	16a.	16b.	Total number of items fulfilling criteria
van den Ende et al., (1996) (Low Intensity)	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	2
van den Ende et al., (1996) (Low Intensity Individualised)	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	4
Häkkinen et al., (2001)	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	0	0	4
Loeppenthin et al., (2022)	1	1	0	1	0	0	0	0	1	0	0	1	0	1	1	1	0	0	0	8
Allam et al., (2018)	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2
Lemmey et al., (2019)	1	1	0	1	0	0	1	1	0	0	0	1	1	1	1	1	1	0	0	11
Ward et al., (2018)	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	0	13
Somers et al., (2020)	0	1	1	1	0	1	0	0	0	0	1	0	1	0	1	1	0	1	0	9
Komatireddy et al., (1997)	1	0	1	1	0	0	0	0	1	1	0	0	1	1	0	0	0	0	0	7

Study	1.	2.	3.	4.	5.	6.	7a.	7b.	8.	9.	10.	11.	12.	13.	14a.	14b.	15.	16a.	16b.	Total number of items fulfilling criteria
Stenström et al., (1996)	1	1	1	1	0	0	0	0	1	1	0	0	1	1	0	0	0	0	0	8
Flint-Wagner et al., (2009)	0	0	1	1	0	1	1	1	0	0	1	0	0	1	1	1	1	0	0	10
Westby et al., (2000)	1	0	1	1	1	0	0	0	0	1	1	0	0	0	1	0	0	1	0	8
Lyngberg et al., (1994)	1	0	1	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	5
Ambrosino et al., (2020)	1	0	1	1	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	6
Häkkinen et al., (1999)	1	0	1	1	0	0	0	0	0	1	0	0	1	0	1	1	0	1	0	8

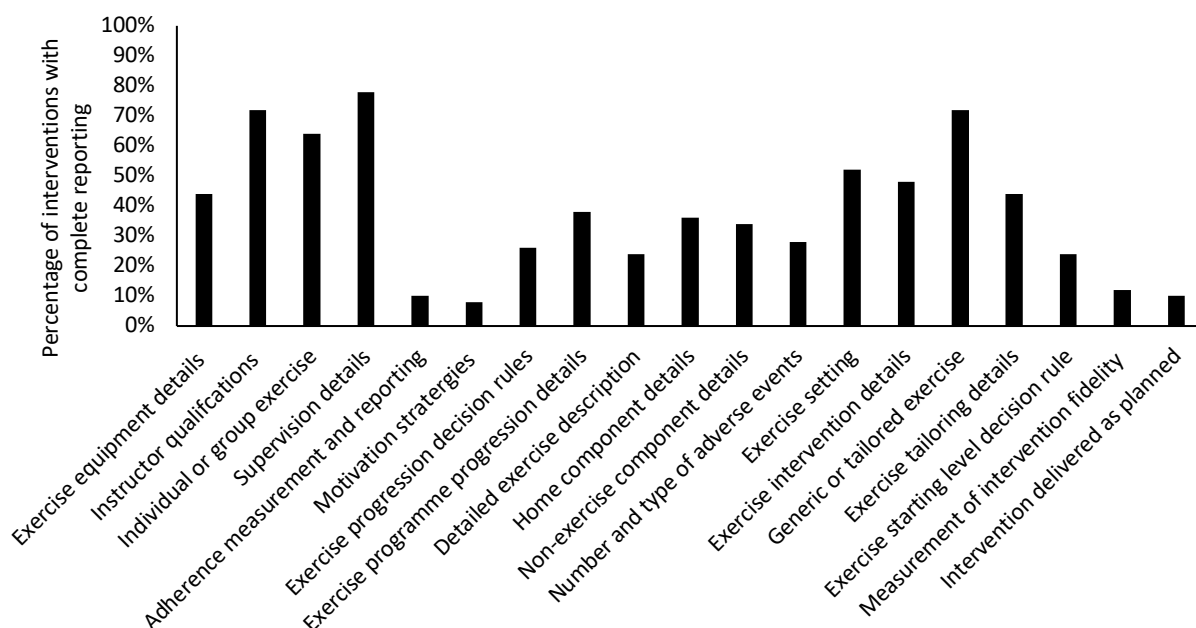


Figure 6.2. Percentage of interventions (out of 50) with complete reporting for each of the Consensus of Exercise Reporting Template checklist statements.

6.4. Discussion

This systematic scoping review summarised the characteristics and the level of reporting of exercise interventions within RCTs for people living with RA utilising the CERT criteria. The reviewed exercise interventions employed a wide variety of exercise protocols and varied supporting components. Overall, most interventions were poorly reported with items being inadequately described, or not described at all.

Most of the interventions involved a combination of supervised aerobic and resistance exercise completed over ~3 sessions per week. The weekly volume of exercise was ~147-162 minutes, most often of a moderate intensity. Recent PA guidelines for people with inflammatory arthritis (Osthoft et al., 2018) recommend 150-300 minutes of moderate-to-vigorous aerobic PA, with 2-3 days a week of strengthening, flexibility and balance exercise. Therefore, the reviewed exercise interventions largely comply with existing public health

recommendations. Interestingly, some interventions used either moderate-to-high intensity or sole high-intensity exercise, while a fewer number of interventions employed low-intensity or low-to-moderate intensity exercise. This could indicate a change in perception of the capabilities of people living with RA to perform moderate and high intensity exercise, which is in line with studies that reported the safety (de Jong et al., 2003, Lemmey et al., 2009) and effectiveness (de Jong et al., 2003, Van den Ende et al., 1996) of high intensity exercise for the RA population.

Over half of the interventions ($n= 26$) reported that exercise was supervised, while six reported partly supervised exercise. Similarly, exercise monitoring was reported in over half of the interventions ($n= 29$), with different strategies such as exercise logs/diaries and in-person monitoring employed. Importantly, supervision and monitoring of physiological parameters during exercise can also confer a sense of safety and individualisation that may lead to improved exercise adherence (Dougherty et al., 2016, Lopes et al., 2023). This is significant as fear and absence of safety are reported barriers for participation in exercise for women with RA (Baxter et al., 2016a). On the other hand, fully supervised exercise interventions may be less cost-effective and more difficult to implement within public health systems (or providers), especially in low or middle-income countries. To combat this, the use of mobile health technology (mHealth) [i.e., applications and wearable fitness devices] may increase the likelihood of providing the perception of safety whilst also improving the feedback process without having to provide expensive full-time supervision (Bannell et al., 2023, Peretti et al., 2017). Less than half of the interventions ($n= 19$) herein reported the use of additional supportive resources, with no interventions specifically utilising modern mHealth technology. As such, future interventions should seek to identify modern cost-effective support resources to combat the aforementioned barriers to exercise faced by people living with RA.

The main finding of this review is that studies examining exercise interventions for people with RA do not adequately describe the content of the exercise interventions. The most poorly reported CERT items in our review included: motivation strategies ($n=4$), adherence measurement and reporting ($n=5$), if the intervention was delivered as planned ($n=5$) and the measurement of intervention fidelity ($n=6$). Interestingly, three of the lowest reported CERT items centre around adherence to the intervention by participants or fidelity of delivery. Intervention fidelity is vital for internal validity and for correct application of the intervention (Moncher and Prinz, 1991) and reporting of adherence is key to understanding the feasibility of interventions. A lack of detailed information in this area may reduce confidence and aptitude to implement exercise interventions in practice.

The most poorly reported item in this review, motivation strategies, is also cause for concern as these strategies have been shown to have moderate additional effects on exercise outcomes as outlined in CERT (Slade et al., 2016). Failure to report motivational strategies in exercise interventions for people with RA could be hugely detrimental given that autonomous motivation has been related to higher self-reported PA in people with RA (Hurkmans et al., 2010). Moreover, failure to report motivational strategies that have been used effectively could lead to interventions failing when replicated due to this missing component which has been shown to effectively combat a well-documented barrier to exercise in people with RA (Veldhuijzen van Zanten et al., 2015a).

It is not totally clear why exercise intervention reporting is poor in studies involving people with RA. Lack of specific guidelines (Osthoff et al., 2018) and established services may affect the design of exercise interventions, which could consequently affect their reporting. Other clinical disciplines (e.g., cardiology or diabetology), in which exercise rehabilitation or referral are well guided and used within routine healthcare, may have more well-defined

exercise intervention protocols, which can positively affect the design and reporting of exercise interventions in research studies. Indeed, in other clinical disciplines (cardiology, hypertension and diabetes) exercise intervention reporting is of a higher quality than that of RA (Hacke et al., 2018, Harwood et al., 2021, Hacke et al., 2022). Whereas the lack of specialised recommendations for people with RA dictates that researchers have no specific guidance to follow and thus nothing specific to draw upon when designing interventions.

The findings from our corpus of interventions are not wholly unique, a recent overview of systematic reviews identified 16 reviews using CERT across a variety of populations (e.g., knee osteoarthritis, stroke etc.) with a median percentage of all appropriately reported CERT items being 24% (Hansford et al., 2022). Somewhat similar to our findings, Hansford et al. (2022) found that measurement of intervention fidelity and whether the intervention was delivered as planned were the worst reported CERT items, with motivation and adherence measurement also being reported poorly. Thus, the poor reporting of these particular items is not exclusive to exercise interventions in RA and may also indicate a widespread issue that must be addressed.

One of the major consequences of a lack of detailed reporting is that it may lead to the apprehension and prevention of the implementation of exercise interventions for people with RA. For clinicians, patients and other decision makers to have confidence to implement effective exercise interventions they must be complete, clear and replicable. Intervention description involves more than providing a *“shopping list of ingredients”* (Hoffmann et al., 2014), with exercise interventions often being complex and multifaceted there is a significant responsibility for researchers to provide complete and replicable intervention details (Bartholdy et al., 2019). There are key features of exercise interventions that can affect efficacy and replicability but, as seen from the results of this review as well as others (Hansford et al., 2022), they are often poorly described or

unreported (e.g., duration, intensity, adherence). Missing or inadequate information will not only affect the confidence of both HCPs and patients but could also render the intervention unimplementable dependent on the level of missing information.

6.4.1. Overall implications for practice and research

To replicate and implement research, published exercise interventions need to be clear, accurate and complete. For example, our review indicates that only 5/50 interventions reported whether interventions were delivered as planned. This leads to findings being unclear and hinders accurate interpretation of intervention results. Similarly, only five interventions reported how adherence was measured and reported, therefore clinicians would be unclear whether participants completed more or less than prescribed.

Overall, 74% of studies scored <10/19, missing key information or a lack of detail which will not improve the known lack of confidence of HCPs (Law et al., 2013, McKenna et al., 2019) to implement research and promote exercise in the RA care pathway. This also has implications for research, as without key intervention details (e.g., intensity of exercise) it is not possible to understand whether an intervention is feasible. This is extremely applicable to people with RA as many may face physical limitations in terms of the duration, intensity and modes of exercise they are able to complete. Likewise, without detailed reporting it is difficult to ascertain which items are associated with outcome measures in research. For example, we do not know the true effect of motivation strategies in exercise interventions in people with RA as this was very poorly reported. Consequently, it may be beneficial for future research studies involving exercise interventions in people with RA, and other clinical populations, to use the CERT both when planning and reporting exercise interventions to be certain all the relevant information is included.

6.4.2. Strengths and limitations

The first strength of our review was the use of the internationally endorsed CERT, which has been shown to be both user-friendly and time-efficient for review purposes (Slade et al., 2018). We also had full agreement between two researchers conducting CERT scoring which increases the reliability of our results. This review is not without limitations, the scope of research included in this review was restricted to investigations using RCTs. Secondly, the process for obtaining missing data from study authors was not performed in this review, however, direct contact of study authors would not have accomplished the objective of assessing an accurate depiction of reporting standards as presented in the published literature which was the main aim of this review.

6.4.3. Conclusion

The quality of reporting for exercise interventions designed for people living with RA is very poor, despite the knowledge that exercise may have widespread beneficial effects on disease symptoms, associated risk factors and general health. Significant improvements to reporting are needed in order to enable quality replication and improve translation of this evidence into clinical practice.

CHAPTER 7: SYNTHESIS OF FINDINGS

7.1. Aims and Objectives

The overarching aim of this body of work was to assess modern approaches to PA prescription and to examine methods that attempt to increase PA in people living with RA via novel approaches. In addition, parameters of cardiovascular health were assessed in order to observe the effects of RA on cardiovascular health.

This synthesis first conveys *reflections from the researcher*, which outline the unique experiences encountered to produce this body of work. This synthesis then goes on to briefly summarise the findings of the four research studies presented within *Chapters 3-6* of this thesis. Finally, the collective findings of the four studies are considered in terms of their translational value and recommendations for future research.

7.2. Reflections

Throughout this section, the researcher will refer to themselves in the first person to discuss reflections from their PhD programme experience.

My PhD programme has provided several challenges, all of which were thought-provoking and fulfilling once overcome. I have learnt a lot during my PhD, both in terms of *academic* and *inter-personal* skills. I have gained an array of skills and learning experiences that have contributed to my development and evolution as a researcher, and as a person. These skills include the co-production of research studies, physiological lab-based testing techniques, remote testing techniques, qualitative data collection and the analysis of data. Moreover, I have improved various *inter-personal* skills which were vital as the first challenge of my PhD, that presented a mere few weeks following registration, was the first national lockdown in response to the COVID-19 pandemic. This resulted in a need for huge adaptations to my planned PhD projects.

The first of these changes was to conduct remote research trials, due to the fast developing and more stringent pandemic restrictions in 2020. As such, the study design and data collection for *Chapter 3* was conducted as part of a larger research team, consisting of three academic staff, two post-doctoral researchers, two PhD candidates, including myself, and an MPhil student. During my time working with this team, I learnt that in order to work effectively with people you need to be able to work in different ways, be adaptable and strive to combine with their unique styles and strengths in an effective manner. As such, communication and compromise were required to operate as a successful and cohesive research team, which was a new dynamic for me after working largely independently in my undergraduate and MPhil research endeavours. The larger research team also meant additional input from colleagues outside of my supervisory team, this of course resulted in a greater level of expert opinion to create this body of work which was a positive outcome. However, more inputs and opinions also proved difficult to navigate. This again helped to me understand different perspectives and then go through a process of weighing up the relevant information and coming to my own resolution. The experiences I gained on this research study not only enhanced my ability to work as part of an effective and proficient team but also led to the development of my ability to use my own initiative and work autonomously.

Due to the longer than initially anticipated and unpredictable, constant fluctuation of COVID-19 restrictions throughout the majority of my PhD tenure, both *Chapters 3 and 4* were remote research trials, utilising similar remote measurement techniques. This involved conducting all aspects of the research over a combination of social media (recruitment) and Zoom/telephone calls (all participant interactions including consent, data collecting, meetings etc.). This largely a new experience as all previous data collection I had been involved in was face-to-face. At times technology can be challenging without

fault or reason, however it can also be of great benefit, allowing you to extend your reach. I believe this style of research trial helped to develop new ways of communicating virtually, which required adaptations from how I may have approached a similar situation in a face-to-face setting. It was vitally important to make sure participants had a full understanding of the testing/measurement procedures which can be difficult over a zoom/telephone call, however again adaptations to my communication style ensured I was able to achieve this. Overall, I believe the remote research trials offered a new and interesting perspective on research, I believe it allowed us to recruit more widely and possibly recruit more people than would have been possible if the trial was a traditional face-to-face research design.

It was also a new experience for me to work with a clinical population. I was very excited by this prospect to begin with, and reflecting at the end of my PhD I feel this was one of favourite aspects of the process. I had to learn how to answer slightly different, more clinically related questions from participants, as well as being reassuring and comforting to any participants who may have been concerned about upregulating their PA or undergoing vascular assessment because of their condition. Feedback from participants from the MOTIVATE RA programme in *Chapter 4* is one of the highlights of this process as I was able to see how much of a positive impact the programme was having on other people's lives. It was these moments that provided extra motivation, especially in moments of challenge and adversity.

My PhD provided many challenges, usually of a different nature to that which I expected. For example, recruitment for Chapter 5 following the ease of COVID-19 restrictions was unexpectedly challenging due to the NHS backlog that had accumulated during the previous 12-18 months. This caused worry regarding recruiting sufficiently for this chapter and as a result I proposed performing a fourth, unplanned research study (*Chapter 6*). The systematic scoping review resulted in further and more diverse skill development, requiring

a different style of thinking and organisation. It became difficult to balance three ongoing studies at one time (*Chapters 4-6*) but, on reflection the addition of the systematic scoping review has allowed me to gain invaluable skills. Navigating COVID-19 and the ensuing restrictions was undoubtedly the biggest challenge I faced during my PhD, along with the various other 'knock-on effects' during this time. Despite feeling overwhelmed at times, I am incredibly proud of the body of work produced during this professionally, and personally, turbulent period.

My PhD programme has required a great level of adaptability and critical thinking, as well as the other necessary skills in order to reach completion. I believe the experiences and skills I have gained over the last four years have led to great improvements in my ability as a researcher.

7.3. Summary of major findings

Chapter 3 demonstrated that an mHealth technology supported intervention has the potential to positively impact exercise behaviour(s). It was also observed that home-based mHealth supported interventions with individualised support were able to increase adherence to unsupervised exercise prescription and consequently increase levels of PA in sedentary individuals. The key components of the MOTIVATE exercise intervention included live visual and haptic feedback via mHealth technology with information regarding timing and HR zones as well as individualised exercise counselling consultations pre-intervention, and at regular intervals throughout the 12-week intervention period (week 4, and week 12).

Chapter 4 expanded upon *Chapter 3* by utilising an adapted mHealth technology supported intervention with individualised support, MOTIVATE RA, to increase PA in people living with RA (a high-risk clinical group). It was observed that an mHealth supported walking

intervention was feasible and acceptable for people living with RA and the preliminary data indicated that such interventions, although lacking statistically significant results, may elicit clinically meaningful change including increases in MVPA levels that have the potential to positively impact the high level of CVD risk observed in this population.

Chapter 5 demonstrated that people living with RA may potentially exhibit both micro- and macrovascular dysfunction, with microvascular dysfunction potentially preceding macrovascular dysfunction and acting as a '*warning signal*', though no statistical significance was present. Meanwhile, it was observed that cerebrovascular function remained unaltered in people living with RA. Future research with higher power is needed to further examine cerebrovascular function in this population in order to fully understand cerebrovascular disease risk.

Chapter 6 highlighted the poor reporting quality of exercise interventions undertaken with people living with RA. The absence of key details and clarity causes issues when considering the feasibility of an intervention, which is extremely important when working with people living with RA as their capacity to complete exercise is often hampered by physical limitations. Moreover, the implications not only include hindering the accurate interpretation of intervention results but also reduce the confidence of HCPs to implement PA and exercise as part of the RA care pathway.

7.4. General discussion of major findings

The section that follows will discuss the major findings in this thesis under the themes of i) Monitoring remote trials and exercise interventions; ii) mHealth technology supported interventions; iii) PA and exercise prescription in RA, and iv) cardiovascular risk in RA.

7.4.1. Monitoring remote trials and exercise interventions

COVID-19 and the ensuing restrictions (Institute for Government, 2021) enforced the adaptation of person facing research. As such, *Chapter 3* was one of the first exercise and PA trials to assess the feasibility of remote measurement techniques. Preceding this, research employing traditional laboratory measurement techniques observed high participant dropout rates of 24-29% (Roy et al., 2018, Jung et al., 2020a, Hesketh et al., 2021a) as opposed to just 16% observed in *Chapter 3*. Moreover, concerns of remote trials leading to poor protocol adherence and missing data (McDermott and Newman, 2021) were also abolished as *Chapter 3* observed over 90% data availability for remote health related measurements. Taken together these data suggest that remote research trials of this nature may provide more complete data than traditional lab-based research. The reasons for this are not fully understood, though participants themselves reported that completing most measurements at home were easy and non-time consuming, with the presence of a researcher not needed as “*everything was explained so well beforehand*” (section 3.3.3.). Though it should be noted that some studies may still require lab-based assessments. Future research should build upon this and seek to examine the multiple the beneficial aspects of remote trials and the underlying reasons behind this.

Previous trials have suggested that health inequality can plague research findings due to the homogenous recruitment of participants (Noonan and Simmons, 2021, Font et al., 2011). Furthermore, research with participants who reside in more rural areas suggested that lack of access to participate in clinical trials may also contribute to the health inequality (Young et al., 2015, Unger et al., 2018). *Chapter 3* demonstrated that remote research trials may overcome this issue as participants lived an average of 36 miles away from the university and there was a spread of deprivation scores in both groups (3 ± 1 AU), thus suggesting a remote study design may help *reach* people who may not typically become

involved in research. Unfortunately, *Chapter 4* did not collect any demographic data or protected characteristics meaning conclusions cannot be drawn as to whether a remote study design contributed to reaching more underrepresented persons. However, it can be postulated that the remote design of *Chapter 4* ($n = 50$) allowed for much higher levels of recruitment of people living with RA in comparison to the more traditional static lab-based study in *Chapter 5* ($n = 15$).

Although only *Chapter 3* assessed the feasibility of monitoring unsupervised home-based PA and exercise, it was also a technique utilised within *Chapter 4*. Data on the quantity and quality of exercise and PA is essential to evaluate the efficacy of an intervention (Shore et al., 2019) and is often poorly reported in interventions involving exercise in people living with RA, as observed in the systematic scoping review detailed in *Chapter 6*. *Chapter 3* was one of the first studies to evaluate the feasibility and fidelity of techniques to monitor adherence and compliance to unsupervised exercise programmes. Optical HR monitoring was employed in both *Chapter 3 and 4* as it had previously been advocated as accurate in providing objective personalised data for responses to exercise (Nes et al., 2017). This approach provided rich data on adherence and compliance in the MOTIVATE (*Chapter 3*) and MOTIVATE RA (*Chapter 4*) groups. However, it should be noted that this approach was less feasible in the online resources group (*Chapter 3*), as less than 50% of participants wore the monitor regularly, additionally in the CC group (*Chapter 4*) it was not feasible within the study design to provide optical heart rate monitors as this would fall outside conventional care. As such future research should attempt to create a comparable, perhaps blinded, measurement of adherence and compliance in order to be allow for comparisons between intervention and control groups.

Accelerometers and GLTEQ questionnaires were also employed in *Chapter 3* to remotely monitor the exercise intervention. The GLTEQ results, though providing excellent data

availability (>90%), demonstrated poor validity for measuring adherence in comparison to the optical HR monitors. Similarly, accelerometers demonstrated poor validity when compared to optical HR monitors for RT and HIIT, likely due to large static components (Matthew, 2005), though correlation statistics were also poor for MICT and VT. As such, *Chapter 4* employed a combination of methods to assess adherence and compliance, in line with the conclusions of *Chapter 3*, in order to obtain the most well-rounded and accurate data.

Overall, *Chapters 3 and 4* have provided a large amount of evidence that supports the feasibility and potential success of conducting and monitoring remote trials and exercise interventions. *Chapter 3* provided a solid foundation, highlighting the feasibility of such techniques, which were then utilised throughout *Chapter 4* with the target clinical population of this thesis.

7.4.2. mHealth technology supported interventions

PA and exercise are vital for general health as well as the prevention and management of long-term conditions (Pedersen and Saltin, 2015), yet still 27.5% of adults worldwide do not meet global PA recommendations (Guthold et al., 2018). Moreover, people living with RA are known to have even higher levels of physical inactivity, with some studies reporting 60-80% of people living with RA as inactive (Sokka et al., 2008). Current management to combat this in the form of ERS often employ unsupervised exercise and are largely concluded to be ineffective (Umpierre et al., 2011, Vemulapalli et al., 2015, Lacroix et al., 2017, Fennell et al., 2016)

Chapters 3 and 4 demonstrated that mHealth technology supported PA and exercise interventions may hold a solution for increasing adherence and compliance and ‘*bridge the gap*’ between unsupervised ERS and supervised interventions. These interventions

ultimately increased levels of PA and positively impacted components of health in both inactive adults and people living with RA. Previous research investigating more traditional ERS had demonstrated adherence levels of 30-47% (Taylor et al., 1998, Hesketh et al., 2021a), however, *Chapter 3* observed an adherence of 113% in the MOTIVATE programme. Further to this compliance to the exercise prescription in MOTIVATE was 73%, clearly demonstrating the exciting potential of mHealth supported interventions to increase adherence and compliance. Increases in accelerometer measured PA in *Chapter 3* were modest, despite high adherence, though this may have owed to the aforementioned (*Section 7.4.1.*) limitations of accelerometry with certain exercise modes employed in this study. Though these changes were in line with previous meta-analyses using technology in self-monitoring interventions (Baskerville et al., 2017, Compennolle et al., 2019). *Chapter 3* demonstrated that the MOTIVATE programme was helpful in mediating positives changes in exercise and PA behaviour which was then expanded on in a clinical population (RA) in *Chapter 4*.

In line with the aim of the study it was demonstrated that people living with RA completed a considerably greater amount of MVPA (103 minutes) than the CC group, though this was not statistically significant. Moreover, the MOTIVATE RA group also exhibited a MCID in both average accelerations (Rowlands et al., 2020) and steps per day (Yates et al., 2019). This provides evidence that the MOITVATE RA walking programme was able to elicit clinically meaningful behaviour change. The finding of a clinically important increase in steps per day is particularly important as it is regularly utilised in clinical settings due to its simplistic nature, easing message delivery of clinicians to their patients. Further research has been conducted assessing clinically important changes in step counts, overriding the widely promoted goal of 10,000 steps per day that has limited evidence to back it up (Lobelo et al., 2018). Moreover, increasing the number of daily steps taken has been shown

to be associated with lower-all cause mortality (Saint-Maurice et al., 2020). Therefore, the finding that the MOTIVATE RA programme elicited a MCID in daily steps is a clear, positive and simplistic take home message. The importance in clarity of findings is highlighted in *Chapter 6* of the thesis, whereby it was demonstrated that poor reporting of exercise interventions in people living with RA may result in poor implementation of such interventions due to a lack of confidence from HCPs in prescribing PA and exercise based in incomplete or inaccurate research (Glasziou et al., 2008)

7.4.3. PA and exercise prescription in RA

In *Chapter 6*, the poor reporting of exercise interventions involving people living with RA was demonstrated by a systematic scoping review. This finding was unsurprising and may be attributed as one of the many factors resulting in low levels of PA observed within the RA population. This is due to the potential *knock-on* effect poor reporting of exercise interventions may have on the confidence of HCPs to prescribe exercise to people living with RA (Law et al., 2013, McKenna et al., 2019). Moreover, this could also affect the confidence of patients to increase their activity.

The interventions implemented in *Chapters 1 and 2* may offer a potential solution to improve the prescription and oversight of PA and exercise in people living with RA. Although these findings alone are unlikely to increase the confidence of HCPs in prescribing exercise, they do represent a viable option for improving exercise prescription. Though, in order for mHealth supported interventions to be effective, it is vital that HCPs are supported in their competency with mHealth related aspects (Moss et al., 2019) so the information being relayed to patients is correct, and all around confidence levels in both HCPs and patients is increased and maintained which would result in meaningful and sustainable behaviour change.

Aside from this, it is vitally important that improvements are made in exercise and PA intervention reporting in people living with RA, especially due to the knowledge that exercise and PA may have widespread benefits on disease symptoms, associated risk factors and general health without adverse effects (Metsios and Lemmey, 2015). Consequently, it may prove beneficial for future research studies to utilise the CERT criteria (used in *Chapter 6* to assess the quality of interventions) when planning and reporting exercise interventions to be sure that all relevant information is included in order to make the research transferable to a clinical setting.

7.4.4. Cardiovascular risk in RA

The increased CVD risk present within the RA population is a huge and continued source of concern. The observed ~50% increased CVD risk in people living with RA compared to the general population (Agca et al., 2017) and the fact that CVD represents the primary cause of mortality in people living with RA indicates that more research and work needs to be undertaken in order to address this issue. The cessation of COVID-19 restrictions allowed for the investigation of the impact of RA on various vascular beds, presented within *Chapter 5* of this thesis. Though not directly connected to the other chapters within this thesis, the lab-based study constitutes important findings as they provide part of the rationale for attempting to find ways to upregulate PA in people living with RA (*Chapter 3 and 4*), as well as investigating an area which may be hindering the ability to increase PA within this population (*Chapter 6*).

Chapter 5, similarly to previous findings, found that microvascular dysfunction may potentially be present in people living with RA (Bordy et al., 2018) and expanded on this by demonstrating that there was more evidence for reduced microvascular function in the forearm than the calf. Previous research has demonstrated that forearm microvascular function is reduced in the RA population (Arosio et al., 2007) but did not compare this with

calf microvascular function. Nevertheless, there is evidence to support this finding in other populations as it has been suggested that the denser network of capillaries in the ventral forearm in comparison with the lateral calf (Pasyk et al., 1989) may result in changes in microvascular function being more prominent in the forearm skin than the leg skin (Smith et al., 2013). It is also known that microvascular dysfunction often precedes dysfunction and subsequent atherosclerosis of larger macro vessels (Gutterman et al., 2016). Although small numbers within the study mean it is difficult to make any firm conclusions, preliminary data do present an interesting proposition that the forearm microvascular dysfunction in people with RA in *Chapter 5*, may potentially be an indicator of future CVD complications.

It was also observed that FMD was reduced in the lower limbs but not in the upper limbs of people living with RA, compared to their non-RA counterparts, though this was not statistically significant. This was perhaps apparent due to the greater susceptibility of the lower limbs to vascular dysfunction and atherosclerosis, as has been demonstrated in previous studies (Vink et al., 2002, Sanada et al., 2005), though not directly in people living with RA. Importantly, most research to date exploring macrovascular function in people living with RA has focused on the assessment of vascular function in the upper limbs (Xu et al., 2017, Fan et al., 2012, Di Minno et al., 2015). Therefore, this observation in *Chapter 5* that lower limb FMD was reduced whereas upper limb FMD was not different from non-RA control participants offers a new perspective to assessing vascular function in people with RA, perhaps suggesting that assessing lower limb vascular function may be more beneficial to detect earlier signs of CVD development.

In contrast to the findings in the micro- and macrovasculature, cerebrovascular vascular function in people living with RA appeared to be unaltered. The RA group did display higher baseline CBFv though this does not necessarily portray better cerebrovascular function and

could be related to higher baseline PETCO₂ (Ainslie and Duffin, 2009) or even due to an increase peripheral vascular resistance (DeLong and Sharma, 2019), though no mechanistic conclusion can be made. Moreover, there were no differences in reactivity to CO₂ in people living with RA, but CA did appear more efficient. This finding was unexpected, though other research studies have reported findings that differed from their original hypothesis in regards to CA (Labrecque et al., 2019). At this time there is insufficient data to establish reference and normative values for the TFA parameters (Panerai et al., 2023) that quantify CA, meaning that it is impossible to comment whether CA in either study group was 'good', 'bad' or 'average'. Additionally, the small sample size and lack of statistical power in the study make it difficult to present a strong conclusion as to the effect of RA on cerebrovascular function.

7.5. Implications of findings

People living with RA face many challenges, from dealing with difficult disease related symptoms to extra-articular manifestations, and beyond. CVD is arguably the most prominent of the wider array of systemic manifestations and concomitant complications experienced by the RA population. Indeed, CVD is the primary cause of mortality in people living with RA (Kitas and Gabriel, 2011). *Chapter 5* of this thesis further highlighted the issue of the lingering risk of CVD with evidence of vascular dysfunction across various vascular beds in people living with RA compared with their non-RA counterparts. Although it is clear from these findings that more research needs to be conducted within the area, particularly in relation to the cerebrovasculature given the emerging evidence of cerebrovascular disease in RA (Wiseman et al., 2016), it is still apparent that vascular dysfunction is present in people living with RA and this indicates susceptibility to future cardiovascular events.

As such it is vital to assess novel ways to try to reduce CVD risk in people living with RA, with a key target area being the upregulation of PA which is notoriously reduced in RA

population (Lee et al., 2012b, Summers et al., 2019). *Chapters 3 and 4*, in combination, demonstrate the ability of mHealth supported interventions to improve PA levels in people living with RA, which have the potential to lead to clinically meaningful changes. The findings of *Chapter 3* represent the foundations for *Chapter 4*. Taken together they demonstrate that remote data collection and remote trials should be viewed as a facilitator to target a wider array of individuals who may typically not have access to clinical trials. Moreover, they provide evidence that remote monitoring of PA and exercise is feasible and allows for greater levels of support to be given during unsupervised exercise, such practices could be adopted within a healthcare setting if proven to be valid, reliable and economically viable.

Furthermore, the evidence that an mHealth technology supported intervention increased levels of PA in people living with RA, and produced clinically important differences, displays the promising potential of incorporating technology into exercise prescription in this population. Again, this is an option which could be utilised in a clinical/healthcare setting if future research was conducted to provide more information on the validity, reliability and economic cost implications of such an intervention. The reporting of such research is of extreme importance, as outlined in *Chapter 6*. The observation that exercise intervention reporting in people living with RA to date is of a poor standard should be considered by future research and steps should be taken to improve this body of research. At present, the implications of poor research reporting may be hindering the implementation of PA and exercise interventions as part of clinical management strategies, preventing possible improvements in CVD risk. This knowledge and the reference to potential ways to improve reporting, such as the use of CERT, could lead to improvements that ultimately increase the likelihood of the uptake of mHealth technology supported interventions within healthcare settings.

7.6. Methodological considerations and limitations

There are a multitude of strengths in the methodology of this thesis. *Chapter 3* was the first exercise and PA intervention study, to our knowledge, to employ a wholly remote study design in which the feasibility of such an approach was assessed. This provided the foundation for *Chapter 4* to be one of the first studies to demonstrate that an mHealth technology supported walking intervention was feasible and acceptable for people living with RA, whilst eliciting improvements in PA that were clinically important. Both of these studies removed known barriers to participation in exercise and arguably improved accessibility and lessen inequality effects in the findings thereby enhancing the quality of the conclusions. Additionally, *Chapter 5* provided a comprehensive assessment of vascular function in people living with RA across multiple vascular beds, including those which have been lesser investigated. Moreover, it appears to be the first study to assess CA within this population which could be an important measurement moving forward with a greater focus on the cerebrovascular health of people living with RA.

Despite these methodological strengths, there are several limitations that should be noted. Firstly, in *Chapters 3 and 4* the remote data collection employed prohibits the ability of the research team to control diet and exercise prior to testing measurements, despite instructions given to participants. Further to this, both chapters employ interventions that require participants to have access to a smart device (i.e., smartphone or tablet) and WiFi/data plan, which could lead to the potential exclusion of individuals from lower socioeconomic groups. Moreover, people with low digital literacy skills may face a greater barrier to entry into mHealth supported interventions. It should also be noted that in *Chapter 4* the majority of participants are middle-aged females, thus caution should be taken when generalising findings as more research may be needed to assess the effect of an mHealth health technology supported walking intervention in males and those in

younger/older age groups. Despite the clear and detailed instructions given to participants in *Chapters 3 and 4* on completion of data collection measurements, it is not known whether participants recorded and reported this data accurately. The research team had planned to invite a local sub-sample of participants into the labs to conduct control testing, but the continuation of COVID-19 restrictions did not allow this. Moreover, there was no follow-up data collected following the 12-week exercise interventions in *Chapter 3*, therefore no conclusions could be made as to whether the exercise intervention strategies were effective in eliciting longer term behaviour change. This was partially rectified in *Chapter 4*, though the three-month follow up assessment employed was optional and thus was only completed by a sub-set of participants. Again, this prevents the ability to be able to make conclusions as to the long-term effect on behaviour change as a result of the mHealth technology supported walking intervention. As such, RCTs employing similar intervention designs should include follow-up assessments, by design, at 3 months and 1-year to investigate medium and long-term behaviour change. Furthermore, the findings in both *Chapters 3 and 4* could be partially skewed as a result of fluctuating government restrictions that aimed to reduce the transmission of COVID-19 during this time. This is especially relevant for *Chapter 4* as people living with RA faced the most challenging restrictions in the form of shielding due to being immunosuppressed and thus considered vulnerable. Finally, *Chapters 3 and 4*, did not include measurements of psychological mechanisms which may have influenced adherence and compliance levels and ultimately lead to behaviour change.

The major limitation of *Chapter 5* was a low sample size meaning that the study was only able to postulate on findings as definitive conclusions could not be made. Moreover, the absence of ultrasound scans of the ICA that would have allowed for better representation of the flow response and dilation of cranial vessels was another limitation. *Chapter 6*,

although having the strength of utilising the internationally endorsed CERT, was not without limitations. The review was restricted to investigations using RCTs and the process for obtaining missing data from study authors was not performed. Though it should be noted, direct contact of study authors would not have accomplished the objective of accurately assessing reporting standards.

7.7. Recommendations for future directions

Based on the evidence reported in this thesis, there are several key areas in which future studies can build upon to further enhance understanding and application:

1. Further examination of the validity of different CRF estimation techniques using mHealth technologies for use with remote clinical research would offer an additional perspective regarding the effectiveness of home-based exercise interventions and their efficacy to decrease all-cause mortality.
2. Future trials should continue to assess the application and effectiveness of mHealth technology supported interventions, such as MOTIVATE and MOTIVATE RA, in order to develop these and maximise adherence to unsupervised exercise in non-active and clinical populations.
3. Further to *Chapters 3 and 4*, studies should routinely employ medium and long-term follow-up assessments to gain more information about the effectiveness of mHealth supported interventions to promote longer term behaviour change.
4. The value of mHealth interventions, as demonstrated in *Chapter 3 and 4*, should be further explored in people with low digital/health literacy. As well as exploring how to optimise mHealth interventions for underserved groups (e.g., IMD, ethnic groups)
5. Based on the findings detailed in *Chapter 5*, future research should focus on further investigation of the cerebrovasculature in people living with RA so that

cerebrovascular disease risk in RA can be greater understood, and care pathways can be developed to aid the management of these risks.

6. SB is a distinct behaviour from PA, and excessive SB has negative physiological effects. Studies that assess breaking up SB time have elicited significant improvements in health outcomes that mirror the upregulation of PA. It is known that people living with RA exhibit disproportionately high periods of time in SB, therefore investigation of the effects of this behaviour modification is warranted in the RA community.
7. *Chapter 6* highlights the need for future research assessing exercise interventions in people living with RA to drastically improve reporting quality and thus raise the quality and application of overall research within the area. Future studies may seek to use CERT when planning and reporting exercise interventions to guarantee the inclusion of key details.

CHAPTER 8: REFERENCES

- AASLID, R. 1986. The Doppler principle applied to measurement of blood flow velocity in cerebral arteries. *Transcranial Doppler Sonography*. Springer.
- AGCA, R., HESLINGA, S. C., ROLLEFSTAD, S., HESLINGA, M., MCINNES, I. B., PETERS, M. J. L., KVIENT, T. K., DOUGADOS, M., RADNER, H., ATZENI, F., PRIMDAHL, J., SÖDERGREN, A., JONSSON, S. W., ROMPAY, J. V., ZABALAN, C., PEDERSEN, T. R., JACOBSSON, L., VLAM, K. D., GONZALEZ-GAY, M. A., SEMB, A. G., KITAS, G. D., SMULDERS, Y. M., SZEKANECZ, Z., SATTAR, N., SYMMONS, D. P. M. & NURMOHAMED, M. T. 2017. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Annals of the Rheumatic Diseases*, 76, 17.
- AINSLIE, P. N. & DUFFIN, J. 2009. Integration of cerebrovascular CO₂ reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 296, R1473-R1495.
- AINSLIE, P. N. & HOILAND, R. L. 2014. Transcranial Doppler ultrasound: valid, invalid, or both? : American Physiological Society Bethesda, MD.
- AINSWORTH, B. E., HASKELL, W. L., HERRMANN, S. D., MECKES, N., BASSETT JR, D. R., TUDOR-LOCKE, C., GREER, J. L., VEZINA, J., WHITT-GLOVER, M. C. & LEON, A. S. 2011. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Medicine & science in sports & exercise*, 43, 1575-1581.
- ALAMANOS, Y., VOULGARI, P. V. & DROSOS, A. A. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Seminars in arthritis and rheumatism*, 2006. Elsevier, 182-188.
- ALETAHA, D., NEOGI, T., SILMAN, A. J., FUNOVITS, J., FELSON, D. T., BINGHAM III, C. O., BIRNBAUM, N. S., BURMESTER, G. R., BYKERK, V. P. & COHEN, M. D. 2010. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis & rheumatism*, 62, 2569-2581.
- ALIVERNINI, S., FIRESTEIN, G. S. & MCINNES, I. B. 2022. The pathogenesis of rheumatoid arthritis. *Immunity*, 55, 2255-2270.
- ALKAABI, J., HO, M., LEVISON, R., PULLAR, T. & BELCH, J. 2003a. Rheumatoid arthritis and macrovascular disease. *Rheumatology*, 42, 292-297.
- ALKAABI, J. K., HO, M., LEVISON, R., PULLAR, T. & BELCH, J. J. F. 2003b. Rheumatoid arthritis and macrovascular disease. *Rheumatology*, 42, 292-297.
- ALLAM, A., KOSTOVA, Z., NAKAMOTO, K. & SCHULZ, P. J. 2015. The effect of social support features and gamification on a Web-based intervention for rheumatoid arthritis patients: randomized controlled trial. *Journal of medical Internet research*, 17, e3510.
- AMERICAN COLLEGE OF SPORTS MEDICINE 2014. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 9th ed. Baltimore, MD: Wolters Kluwer; 2014.
- .
- AMIN, A., MERZA, R., MOHAMMAD, K., AMIN, O. S. M. & ABDULLAH, R. 2014. Rheumatoid Arthritis and the Ankle-Brachial Pressure Index: Any Association? *Cukurova Medical Journal*, 39, 83-90.
- AMMAR, A., BRACH, M., TRABELSI, K., CHTOUROU, H., BOUKHRIS, O., MASMOUDI, L., BOUAZIZ, B., BENTLAGE, E., HOW, D., AHMED, M., MÜLLER, P., MÜLLER, N., ALOUI, A., HAMMOUDA, O., PAINEIRAS-DOMINGOS, L. L., BRAAKMAN-JANSEN, A.,

- WREDE, C., BASTONI, S., PERNAMBUCO, C. S., MATARUNA, L., TAHERI, M., IRANDOUST, K., KHACHAREM, A., BRAGAZZI, N. L., CHAMARI, K., GLENN, J. M., BOTT, N. T., GARGOURI, F., CHAARI, L., BATATIA, H., ALI, G. M., ABDELKARIM, O., JARRAYA, M., EL ABED, K., SOUISSI, N., VAN GEMERT-PIJNEN, L., RIEMANN, B. L., RIEMANN, L., MOALLA, W., GÓMEZ-RAJA, J., EPSTEIN, M., SANDERMAN, R., SCHULZ, S. V. W., JERG, A., AL-HORANI, R., MANSI, T., JMAIL, M., BARBOSA, F., FERREIRA-SANTOS, F., ŠIMUNIČ, B., PIŠOT, R., GAGGIOLI, A., BAILEY, S. J., STEINACKER, J. M., DRISS, T., HOEKELMANN, A. & CONSORTIUM, O. B. O. T. E.-C. 2020. Effects of COVID-19 Home Confinement on Eating Behaviour and Physical Activity: Results of the ECLB-COVID19 International Online Survey. *Nutrients*, 12, 1583.
- ANDERSON, T. J. 1999. Assessment and treatment of endothelial dysfunction in humans. *Journal of the American College of Cardiology*, 34, 631-638.
- ARGENT, R., DALY, A. & CAULFIELD, B. 2018. Patient involvement with home-based exercise programs: can connected health interventions influence adherence? *JMIR mHealth and uHealth*, 6, e8518.
- ARNETT, F. C., EDWORTHY, S. M., BLOCH, D. A., MCSHANE, D. J., FRIES, J. F., COOPER, N. S., HEALEY, L. A., KAPLAN, S. R., LIANG, M. H. & LUTHRA, H. S. 1988. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 31, 315-324.
- AROSIO, E., DE MARCHI, S., RIGONI, A., PRIOR, M., DELVA, P. & LECHI, A. 2007. Forearm haemodynamics, arterial stiffness and microcirculatory reactivity in rheumatoid arthritis. *Journal of hypertension*, 25, 1273-1278.
- ASTLEY, C., PINTO, A. J., BONFÁ, E., DA SILVA, C. A. A. & GUALANO, B. 2021. Gaps on rheumatologists' knowledge of physical activity. *Clinical rheumatology*, 40, 2907-2911.
- ATKINSON, G. & BATTERHAM, A. M. 2013. Allometric scaling of diameter change in the original flow-mediated dilation protocol. *Atherosclerosis*, 226, 425-427.
- ATKINSON, G., BATTERHAM, A. M., THIJSEN, D. H. & GREEN, D. J. 2013. A new approach to improve the specificity of flow-mediated dilation for indicating endothelial function in cardiovascular research. *Journal of hypertension*, 31, 287-291.
- AVIÑA - ZUBIETA, J. A., CHOI, H. K., SADATSAFAVI, M., ETMINAN, M., ESDAILE, J. M. & LACAILLE, D. 2008. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta - analysis of observational studies. *Arthritis Care & Research*, 59, 1690-1697.
- BACHMANN, C., OESCH, P. & BACHMANN, S. 2018. Recommendations for improving adherence to home-based exercise: a systematic review. *Physikalische Medizin, Rehabilitationsmedizin, Kurortmedizin*, 28, 20-31.
- BACIGALUPO, R., CUDD, P., LITTLEWOOD, C., BISSELL, P., HAWLEY, M. & BUCKLEY WOODS, H. 2013. Interventions employing mobile technology for overweight and obesity: an early systematic review of randomized controlled trials. *Obesity reviews*, 14, 279-291.
- BAGHDADI, L. R., WOODMAN, R. J., SHANAHAN, E. M. & MANGONI, A. A. 2015. The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. *PloS one*, 10, e0117952-e0117952.
- BAHEKAR, A. A., SINGH, S., SAHA, S., MOLNAR, J. & ARORA, R. 2007. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *American heart journal*, 154, 830-837.

- BAILEY, D. M., MARLEY, C. J., BRUGNIAUX, J. V., HODSON, D., NEW, K. J., OGOH, S. & AINSLIE, P. N. 2013. Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. *Stroke*, 44, 3235-3238.
- BAILLET, A., VAILLANT, M., GUINOT, M., JUVIN, R. & GAUDIN, P. 2011. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. *Rheumatology*, 51, 519-527.
- BAILLET, A., ZEBOULON, N., GOSSEC, L., COMBESCURE, C., BODIN, L. A., JUVIN, R., DOUGADOS, M. & GAUDIN, P. 2010. Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: meta - analysis of randomized controlled trials. *Arthritis care & research*, 62, 984-992.
- BAKKER, S. L., DE LEEUW, F.-E., DEN HEIJER, T., KOUDSTAAL, P. J., HOFMAN, A. & BRETELER, M. M. 2004. Cerebral haemodynamics in the elderly: the rotterdam study. *Neuroepidemiology*, 23, 178-184.
- BALCHIN, C., TAN, A. L., WILSON, O. J., MCKENNA, J. & STAVROPOULOS-KALINOGLU, A. 2022. Participation in physical activity decreased more in people with rheumatoid arthritis than the general population during the COVID-19 lockdown: a cross-sectional study. *Rheumatology international*, 42, 241-250.
- BANDURA, A. 1986. Social foundations of thought and action. *Englewood Cliffs, NJ*, 1986.
- BANDURA, A. 1997. The nature and structure of self-efficacy. *Self-efficacy: the exercise of control*. New York, NY: WH Freeman and Company, 37-78.
- BANNELL, D. J., FRANCE-RATCLIFFE, M., BUCKLEY, B. J. R., CROZIER, A., DAVIES, A. P., HESKETH, K. L., JONES, H., COCKS, M., SPRUNG, V. S. & TEAM, M. 2023. Adherence to unsupervised exercise in sedentary individuals: A randomised feasibility trial of two mobile health interventions. *Digital health*, 9, 20552076231183552.
- BARTHOLDY, C., NIELSEN, S., WARMING, S., HUNTER, D., CHRISTENSEN, R. & HENRIKSEN, M. 2019. Poor replicability of recommended exercise interventions for knee osteoarthritis: a descriptive analysis of evidence informing current guidelines and recommendations. *Osteoarthritis and cartilage*, 27, 3-22.
- BASHSHUR, R. L., SHANNON, G. W., SMITH, B. R., ALVERSON, D. C., ANTONIOTTI, N., BARSAN, W. G., BASHSHUR, N., BROWN, E. M., COYE, M. J. & DOARN, C. R. 2014. The empirical foundations of telemedicine interventions for chronic disease management. *Telemedicine and e-Health*, 20, 769-800.
- BASKERVILLE, R., RICCI - CABELLO, I., ROBERTS, N. & FARMER, A. 2017. Impact of accelerometer and pedometer use on physical activity and glycaemic control in people with type 2 diabetes: a systematic review and meta - analysis. *Diabetic medicine*, 34, 612-620.
- BAXTER, S., SMITH, C., TREHARNE, G., STEBBINGS, S. & HALE, L. 2016a. What are the perceived barriers, facilitators and attitudes to exercise for women with rheumatoid arthritis? A qualitative study. *Disability and rehabilitation*, 38, 773-780.
- BAXTER, S. V., HALE, L. A., STEBBINGS, S., GRAY, A. R., SMITH, C. M. & TREHARNE, G. J. 2016b. Walking is a Feasible Physical Activity for People with Rheumatoid Arthritis: A Feasibility Randomized Controlled Trial. *Musculoskeletal Care*, 14, 47-56.
- BELL, K., HENDRY, G. & STEULTJENS, M. 2022. Physical activity and sedentary behavior in people with inflammatory joint disease: a cross - sectional study. *Arthritis Care & Research*, 74, 493-500.

- BENNETT, H., PARFITT, G., DAVISON, K. & ESTON, R. 2016. Validity of submaximal step tests to estimate maximal oxygen uptake in healthy adults. *Sports Medicine*, 46, 737-750.
- BILLINGHAM, S. A., WHITEHEAD, A. L. & JULIOUS, S. A. 2013. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC medical research methodology*, 13, 1-6.
- BISWAS, A., OH, P. I., FAULKNER, G. E., BAJAJ, R. R., SILVER, M. A., MITCHELL, M. S. & ALTER, D. A. 2015. Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults. *Annals of Internal Medicine*, 162, 123-132.
- BLACK, M. A., CABLE, N. T., THIJSEN, D. H. J. & GREEN, D. J. 2008. Importance of Measuring the Time Course of Flow-Mediated Dilatation in Humans. *Hypertension*, 51, 203-210.
- BLAIR, S. N. 2009. Physical inactivity: the biggest public health problem of the 21st century. *British Journal of Sports Medicine*, 43, 1.
- BLAND, J. M. & ALTMAN, D. 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *The lancet*, 327, 307-310.
- BONIFACE, G., GANDHI, V., NORRIS, M., WILLIAMSON, E., KIRTLEY, S. & O'CONNELL, N. E. 2020. A systematic review exploring the evidence reported to underpin exercise dose in clinical trials of rheumatoid arthritis. *Rheumatology*, 59, 3147-3157.
- BOOTH, F. W., ROBERTS, C. K. & LAYE, M. J. 2012. Lack of exercise is a major cause of chronic diseases. *Comprehensive physiology*, 2, 1143.
- BORDY, R., QUIRIÉ, A., MARIE, C., WENDLING, D., TOTOSON, P. & DEMOUGEOT, C. 2020. Vascular arginase is a relevant target to improve cerebrovascular endothelial dysfunction in rheumatoid arthritis: evidence from the model of adjuvant-induced arthritis. *Translational stroke research*, 11, 4-15.
- BORDY, R., TOTOSON, P., PRATI, C., MARIE, C., WENDLING, D. & DEMOUGEOT, C. 2018. Microvascular endothelial dysfunction in rheumatoid arthritis. *Nature Reviews Rheumatology*, 14, 404-420.
- BORG, G. 1998. *Borg's perceived exertion and pain scales*, Human kinetics.
- BOWDEN DAVIES, K. A., PICKLES, S., SPRUNG, V. S., KEMP, G. J., ALAM, U., MOORE, D. R., TAHRANI, A. A. & CUTHBERTSON, D. J. 2019. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. *Therapeutic advances in endocrinology and metabolism*, 10, 2042018819888824.
- BOWDEN DAVIES, K. A., SPRUNG, V. S., NORMAN, J. A., THOMPSON, A., MITCHELL, K. L., HALFORD, J. C., HARROLD, J. A., WILDING, J. P., KEMP, G. J. & CUTHBERTSON, D. J. 2018. Short-term decreased physical activity with increased sedentary behaviour causes metabolic derangements and altered body composition: effects in individuals with and without a first-degree relative with type 2 diabetes. *Diabetologia*, 61, 1282-1294.
- BOYLE, L. J., CREDEUR, D. P., JENKINS, N. T., PADILLA, J., LEIDY, H. J., THYFAULT, J. P. & FADEL, P. J. 2013. Impact of reduced daily physical activity on conduit artery flow-mediated dilation and circulating endothelial microparticles. *Journal of applied physiology*, 115, 1519-1525.
- BRANNAN, M., BERNARDOTTO, M., CLARKE, N. & VARNEY, J. 2019. Moving healthcare professionals—a whole system approach to embed physical activity in clinical practice. *BMC medical education*, 19, 1-7.

- BRASSARD, P., ROY, M.-A., BURMA, J. S., LABRECQUE, L. & SMIRL, J. D. 2023. Quantification of dynamic cerebral autoregulation: welcome to the jungle! *Clinical Autonomic Research*, 1-20.
- BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative research in psychology*, 3, 77-101.
- BRAUN, V. & CLARKE, V. 2012. Thematic analysis. *APA handbook of research methods in psychology, Vol 2: Research designs: Quantitative, qualitative, neuropsychological, and biological*. Washington, DC, US: American Psychological Association.
- BRICKWOOD, K.-J., WATSON, G., O'BRIEN, J. & WILLIAMS, A. D. 2019. Consumer-based wearable activity trackers increase physical activity participation: systematic review and meta-analysis. *JMIR mHealth and uHealth*, 7, e11819.
- BRITISH HEART FOUNDATION NATIONAL CENTRE 2010. A Toolkit for the Design, Implementation and Evaluation of Exercise Referral Schemes. . *Loughbrough, UK: BHF Physical Activity and Health*.
- BRODIN, N., EURENIUS, E., JENSEN, I., NISELL, R., OPAVA, C. H. & GROUP, P. S. 2008. Coaching patients with early rheumatoid arthritis to healthy physical activity: a multicenter, randomized, controlled study. *Arthritis Care & Research*, 59, 325-331.
- BROWN, A., QUINN, M., KARIM, Z., CONAGHAN, P., PETERFY, C., HENSOR, E., WAKEFIELD, R., O'CONNOR, P. & EMERY, P. 2006. Presence of significant synovitis in rheumatoid arthritis patients with disease - modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 54, 3761-3773.
- BROWN, R., RANDHAWA, A., CANNING, K., FUNG, M., JIANDANI, D., WHARTON, S. & KUK, J. 2018. Waist circumference at five common measurement sites in normal weight and overweight adults: which site is most optimal? *Clinical Obesity*, 8, 21-29.
- BULLOCK, J., RIZVI, S. A., SALEH, A. M., AHMED, S. S., DO, D. P., ANSARI, R. A. & AHMED, J. 2019. Rheumatoid arthritis: a brief overview of the treatment. *Medical Principles and Practice*, 27, 501-507.
- CAI, Y., ZHANG, J., LIANG, J., XIAO, M., ZHANG, G., JING, Z., LV, L., NAN, K. & DANG, X. 2023. The burden of rheumatoid arthritis: findings from the 2019 global burden of diseases study and forecasts for 2030 by Bayesian age-period-cohort analysis. *Journal of Clinical Medicine*, 12, 1291.
- CAMBRIDGE, G., ACHARYA, J., COOPER, J. A., EDWARDS, J. C. & HUMPHRIES, S. E. 2013. Antibodies to citrullinated peptides and risk of coronary heart disease. *Atherosclerosis*, 228, 243-246.
- CARRIER, B., CREER, A., WILLIAMS, L. R., HOLMES, T. M., JOLLEY, B. D., DAHL, S., WEBER, E. & STANDIFIRD, T. 2020. Validation of garmin fenix 3 HR fitness tracker biomechanics and metabolics (VO2max). *Journal for the Measurement of Physical Behaviour*, 3, 331-337.
- CARTER, S., HARTMAN, Y., HOLDER, S., THIJSEN, D. H. & HOPKINS, N. D. 2017. Sedentary behavior and cardiovascular disease risk: mediating mechanisms. *Exercise and sport sciences reviews*, 45, 80-86.
- CASAS, J., SHAH, T., HINGORANI, A., DANESH, J. & PEPYS, M. 2008. C - reactive protein and coronary heart disease: a critical review. *Journal of internal medicine*, 264, 295-314.
- CASPERSEN, C. J., POWELL, K. E. & CHRISTENSON, G. M. 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public health reports (Washington, D.C. : 1974)*, 100, 126-131.

- CHANG, C.-L., CHIU, C.-M., HUNG, S.-Y., LEE, S.-H., LEE, C.-S., HUANG, C.-M. & CHOU, C.-L. 2009. The relationship between quality of life and aerobic fitness in patients with rheumatoid arthritis. *Clinical Rheumatology*, 28, 685-691.
- CHEN, C.-I., WANG, L., WEI, W., YUCE, H. & PHILLIPS, K. 2018. Burden of rheumatoid arthritis among US Medicare population: co-morbidities, health-care resource utilization and costs. *Rheumatology advances in practice*, 2, rky005.
- CHOY, E., GANESHALINGAM, K., SEMB, A. G., SZEKANECZ, Z. & NURMOHAMED, M. 2014. Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. *Rheumatology*, 53, 2143-2154.
- CHURCH, T. S. & BLAIR, S. N. 2009. When will we treat physical activity as a legitimate medical therapy...even though it does not come in a pill? *British Journal of Sports Medicine*, 43, 80.
- CIFTCI, O., YILMAZ, S., TOPCU, S., CALISKAN, M., GULLU, H., ERDOGAN, D., PAMUK, B. O., YILDIRIR, A. & MUDERRISOGLU, H. 2008. Impaired coronary microvascular function and increased intima-media thickness in rheumatoid arthritis. *Atherosclerosis*, 198, 332-337.
- CLAASSEN, J. A., LEVINE, B. D. & ZHANG, R. 2009a. Dynamic cerebral autoregulation during repeated squat-stand maneuvers. *Journal of applied physiology*, 106, 153-160.
- CLAASSEN, J. A., MEEL-VAN DEN ABELEN, A. S., SIMPSON, D. M. & PANERAI, R. B. 2016. Transfer function analysis of dynamic cerebral autoregulation: A white paper from the International Cerebral Autoregulation Research Network. *Journal of Cerebral Blood Flow & Metabolism*, 36, 665-680.
- CLAASSEN, J. A. H. R., LEVINE, B. D. & ZHANG, R. 2009b. Dynamic cerebral autoregulation during repeated squat-stand maneuvers. *Journal of Applied Physiology*, 106, 153-160.
- CLAPP, B. R., HINGORANI, A. D., KHARBANDA, R. K., MOHAMED-ALI, V., STEPHENS, J. W., VALLANCE, P. & MACALLISTER, R. J. 2004. Inflammation-induced endothelial dysfunction involves reduced nitric oxide bioavailability and increased oxidant stress. *Cardiovascular research*, 64, 172-178.
- CLARKE, V., BRAUN, V. & HAYFIELD, N. 2015. Thematic analysis. *Qualitative psychology: A practical guide to research methods*, 222, 248.
- COHEN, M. P. 1998. Determining sample sizes for surveys with data analyzed by hierarchical linear models. *Journal of Official Statistics*, 14, 267.
- COLLABORATION, E. R. F. 2010. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *The Lancet*, 375, 132-140.
- COMPERNOLLE, S., DESMET, A., POPPE, L., CROMBEZ, G., DE BOURDEAUDHUIJ, I., CARDON, G., VAN DER PLOEG, H. P. & VAN DYCK, D. 2019. Effectiveness of interventions using self-monitoring to reduce sedentary behavior in adults: a systematic review and meta-analysis. *International Journal of Behavioral Nutrition and Physical Activity*, 16, 1-16.
- CONN, V. S., HAFDAHL, A. R., MINOR, M. A. & NIELSEN, P. J. Physical activity interventions among adults with arthritis: meta-analysis of outcomes. *Seminars in arthritis and rheumatism*, 2008. Elsevier, 307-316.
- COONEY, J. K., LAW, R.-J., MATSCHKE, V., LEMMEY, A. B., MOORE, J. P., AHMAD, Y., JONES, J. G., MADDISON, P. & THOM, J. M. 2011. Benefits of Exercise in Rheumatoid Arthritis. *Journal of Aging Research*, 2011, 681640.

- CRACOWSKI, J.-L., MINSON, C. T., SALVAT-MELIS, M. & HALLIWILL, J. R. 2006. Methodological issues in the assessment of skin microvascular endothelial function in humans. *Trends in pharmacological sciences*, 27, 503-508.
- CRAMP, F., BERRY, J., GARDINER, M., SMITH, F. & STEPHENS, D. 2013. Health behaviour change interventions for the promotion of physical activity in rheumatoid arthritis: a systematic review. *Musculoskeletal care*, 11, 238-247.
- CROSS, M., SMITH, E., HOY, D., CARMONA, L., WOLFE, F., VOS, T., WILLIAMS, B., GABRIEL, S., LASSERE, M. & JOHNS, N. 2014. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Annals of the rheumatic diseases*.
- CROWSON, C., MYASOEDOVA, E. & ROGER, V. 2009. Does the Framingham Score underestimate cardiovascular risk in rheumatoid arthritis? *Arthritis Rheum*, 60, S264.
- CROWSON, C. S., ROLLEFSTAD, S., IKDAHL, E., KITAS, G. D., VAN RIEL, P. L., GABRIEL, S. E., MATTESON, E. L., KVIEN, T. K., DOUGLAS, K. & SANDOO, A. 2018. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Annals of the rheumatic diseases*, 77, 48-54.
- DAVERGNE, T., PALLOT, A., DECHARTRES, A., FAUTREL, B. & GOSSEC, L. 2019. Use of wearable activity trackers to improve physical activity behavior in patients with rheumatic and musculoskeletal diseases: a systematic review and meta - analysis. *Arthritis care & research*, 71, 758-767.
- DE HEUS, R. A., DE JONG, D. L., SANDERS, M. L., VAN SPIJKER, G. J., OUDEGEEST-SANDER, M. H., HOPMAN, M. T., LAWLOR, B. A., OLDE RIKKERT, M. G. & CLAASSEN, J. A. 2018. Dynamic regulation of cerebral blood flow in patients with Alzheimer disease. *Hypertension*, 72, 139-150.
- DE JONG, Z., MUNNEKE, M., ZWINDERMAN, A. H., KROON, H. M., JANSEN, A., RONDAY, K. H., VAN SCHAARDENBURG, D., DIJKMANS, B. A., VAN DEN ENDE, C. H. & BREEDVELD, F. C. 2003. Is a long - term high - intensity exercise program effective and safe in patients with rheumatoid arthritis?: results of a randomized controlled trial. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 48, 2415-2424.
- DEANE, K. D., DEMORUELLE, M. K., KELMENSEN, L. B., KUHN, K. A., NORRIS, J. M. & HOLERS, V. M. 2017. Genetic and environmental risk factors for rheumatoid arthritis. *Best practice & research Clinical rheumatology*, 31, 3-18.
- DELONG, C. & SHARMA, S. 2019. Physiology, peripheral vascular resistance.
- DEPARTMENT OF HEALTH 2001. Exercise Referral Systems: A National Quality Assurance Framework,. *London, UK*.
- DHSC, D. O. H. S. C. 2019. UK Chief Medical Officers' Physical Activity Guidelines.
- DI MINNO, M. N. D., AMBROSINO, P., LUPOLI, R., DI MINNO, A., TASSO, M., PELUSO, R. & TREMOLI, E. 2015. Clinical assessment of endothelial function in patients with rheumatoid arthritis: a meta-analysis of literature studies. *European journal of internal medicine*, 26, 835-842.
- DING, D., LAWSON, K. D., KOLBE-ALEXANDER, T. L., FINKELSTEIN, E. A., KATZMARZYK, P. T., VAN MECHELEN, W. & PRATT, M. 2016. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *The Lancet*, 388, 1311-1324.
- DOUGHERTY, C. M., LUTTRELL, M. N., BURR, R. L., KIM, M. & HASKELL, W. L. 2016. Adherence to an aerobic exercise intervention after an implantable cardioverter defibrillator (ICD). *Pacing and Clinical Electrophysiology*, 39, 128-139.

- DURCAN, L., WILSON, F. & CUNNANE, G. 2014. The Effect of Exercise on Sleep and Fatigue in Rheumatoid Arthritis: A Randomized Controlled Study. *The Journal of Rheumatology*, 41, 1966-1973.
- EAMES, M., BEN-SHLOMO, Y. & MARMOT, M. G. 1993. Social deprivation and premature mortality: regional comparison across England. *British Medical Journal*, 307, 1097-1102.
- EAPEN, Z. J. & PETERSON, E. D. 2015. Can mobile health applications facilitate meaningful behavior change?: time for answers. *Jama*, 314, 1236-1237.
- EKELUND, U., STEENE-JOHANNESSEN, J., BROWN, W. J., FAGERLAND, M. W., OWEN, N., POWELL, K. E., BAUMAN, A. & LEE, I. M. 2016. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *The Lancet*, 388, 1302-1310.
- ELDRIDGE, S. M., CHAN, C. L., CAMPBELL, M. J., BOND, C. M., HOPEWELL, S., THABANE, L. & LANCASTER, G. A. 2016. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *bmj*, 355.
- ENGELKE, K. A., HALLIWILL, J. R., PROCTOR, D. N., DIETZ, N. M. & JOYNER, M. J. 1996. Contribution of nitric oxide and prostaglandins to reactive hyperemia in the human forearm. *Journal of Applied Physiology*, 81, 1807-1814.
- ENGLAND, B. R., THIELE, G. M., ANDERSON, D. R. & MIKULS, T. R. 2018. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *Bmj*, 361.
- EVERETT, B. M., PRADHAN, A. D., SOLOMON, D. H., PAYNTER, N., MACFADYEN, J., ZAHARRIS, E., GUPTA, M., CLEARFIELD, M., LIBBY, P. & HASAN, A. A. 2013. Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. *American heart journal*, 166, 199-207. e15.
- EZZAT, A. M., MACPHERSON, K., LEESE, J. & LI, L. C. 2015. The effects of interventions to increase exercise adherence in people with arthritis: a systematic review. *Musculoskeletal Care*, 13, 1-18.
- FAN, C.-Y., ZHANG, Z.-Y., MEI, Y.-F., WU, C.-J. & SHEN, B.-Z. 2012. Impaired brachial artery flow-mediated dilation and increased carotid intima-media thickness in rheumatoid arthritis patients. *Chinese Medical Journal*, 125, 832-837.
- FELDMAN, D. I., THEODORE ROBISON, W., PACOR, J. M., CADDELL, L. C., FELDMAN, E. B., DEITZ, R. L., FELDMAN, T., MARTIN, S. S., NASIR, K. & BLAHA, M. J. 2018. Harnessing mHealth technologies to increase physical activity and prevent cardiovascular disease. *Clinical cardiology*, 41, 985-991.
- FENNELL, C., PEROUTKY, K. & GLICKMAN, E. 2016. Effects of supervised training compared to unsupervised training on physical activity, muscular endurance, and cardiovascular parameters. *MOJ Orthop Rheumatol*, 5, 00184.
- FIERSTRA, J., SOBCZYK, O., BATTISTI-CHARBONNEY, A., MANDELL, D. M., POUBLANC, J., CRAWLEY, A. P., MIKULIS, D. J., DUFFIN, J. & FISHER, J. A. 2013. Measuring cerebrovascular reactivity: what stimulus to use? *The Journal of Physiology*, 591, 5809-5821.
- FIGUS, F. A., PIGA, M., AZZOLIN, I., MCCONNELL, R. & IAGNOCCO, A. 2021. Rheumatoid arthritis: extra-articular manifestations and comorbidities. *Autoimmunity reviews*, 20, 102776.
- FIRESTEIN, G. S. 2003. Evolving concepts of rheumatoid arthritis. *Nature*, 423, 356-361.
- FOLINO, A. F. 2007. Cerebral autoregulation and syncope. *Progress in cardiovascular diseases*, 50, 49-80.

- FONT, J. C., HERNÁNDEZ-QUEVEDO, C. & MCGUIRE, A. 2011. Persistence despite action? Measuring the patterns of health inequality in England (1997–2007). *Health Policy*, 103, 149-159.
- FOSTER, W., CARRUTHERS, D., LIP, G. Y. & BLANN, A. D. 2010. Inflammation and microvascular and macrovascular endothelial dysfunction in rheumatoid arthritis: effect of treatment. *The Journal of rheumatology*, 37, 711-716.
- FREDRIKSSON, I., LARSSON, M. & STRÖMBERG, T. 2010. Model-based quantitative laser Doppler flowmetry in skin. *Journal of biomedical optics*, 15, 057002-057002-12.
- FURBY, H. V., WARNERT, E. A., MARLEY, C. J., BAILEY, D. M. & WISE, R. G. 2020. Cardiorespiratory fitness is associated with increased middle cerebral arterial compliance and decreased cerebral blood flow in young healthy adults: a pulsed ASL MRI study. *Journal of Cerebral Blood Flow & Metabolism*, 40, 1879-1889.
- GARRY, P., EZRA, M., ROWLAND, M., WESTBROOK, J. & PATTINSON, K. 2015. The role of the nitric oxide pathway in brain injury and its treatment—from bench to bedside. *Experimental neurology*, 263, 235-243.
- GIBOFSKY, A. 2012. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *The American journal of managed care*, 18, S295-302.
- GILBERT, A. L., LEE, J., EHRLICH-JONES, L., SEMANIK, P. A., SONG, J., PELLEGRINI, C. A., PINTO, D., DUNLOP, D. D. & CHANG, R. W. A randomized trial of a motivational interviewing intervention to increase lifestyle physical activity and improve self-reported function in adults with arthritis. *Seminars in arthritis and rheumatism*, 2018. Elsevier, 732-740.
- GILES, J. T., POST, W. S., BLUMENTHAL, R. S., POLAK, J., PETRI, M., GELBER, A. C., SZKLO, M. & BATHON, J. M. 2011. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. *Arthritis & Rheumatism*, 63, 3216-3225.
- GLASZIOU, P., MEATS, E., HENEGHAN, C. & SHEPPERD, S. 2008. What is missing from descriptions of treatment in trials and reviews? *Bmj*, 336, 1472-1474.
- GODIN, G. & SHEPHARD, R. 1997. Godin leisure-time exercise questionnaire. *Med Sci Sports Exerc*, 29, S36-S38.
- GODIN, G. & SHEPHARD, R. J. 1985. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci*, 10, 141-6.
- GONZALEZ, M. A. & SELWYN, A. P. 2003. Endothelial function, inflammation, and prognosis in cardiovascular disease. *The American journal of medicine*, 115, 99-106.
- GOODSON, N. J., SYMMONS, D. P., SCOTT, D. G., BUNN, D., LUNT, M. & SILMAN, A. J. 2005. Baseline levels of C - reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten - year followup study of a primary care-based inception cohort. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 52, 2293-2299.
- GREEN, D. J., JONES, H., THIJSEN, D., CABLE, N. T. & ATKINSON, G. 2011. Flow-Mediated Dilation and Cardiovascular Event Prediction. *Hypertension*, 57, 363-369.
- GREMESE, E. & FERRACCIOLI, G. 2011. The metabolic syndrome: the crossroads between rheumatoid arthritis and cardiovascular risk. *Autoimmunity reviews*, 10, 582-589.
- GUTHOLD, R., STEVENS, G. A., RILEY, L. M. & BULL, F. C. 2018. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. *The Lancet Global Health*, 6, e1077-e1086.
- GUTTERMAN, D. D., CHABOWSKI, D. S., KADLEC, A. O., DURAND, M. J., FREED, J. K., AIT-AISSA, K. & BEYER, A. M. 2016. The human microcirculation: regulation of flow and beyond. *Circulation research*, 118, 157-172.

- GYURCSIK, N. C., BRAWLEY, L. R., SPINK, K. S. & SESSFORD, J. D. 2013. Meeting physical activity recommendations: self-regulatory efficacy characterizes differential adherence during arthritis flares. *Rehabilitation Psychology*, 58, 43.
- HACKE, C., NUNAN, D. & WEISSER, B. 2018. Do exercise trials for hypertension adequately report interventions? A reporting quality study. *International journal of sports medicine*, 39, 902-908.
- HACKE, C., SCHREIBER, J. & WEISSER, B. 2022. Application of the templates TIDieR and CERT reveal incomplete reporting and poor replicability of exercise interventions for type 2 diabetes mellitus. *Current Diabetes Reviews*, 18, 97-109.
- HALL, J., SKEVINGTON, S. M., MADDISON, P. J. & CHAPMAN, K. 1996. A randomized and controlled trial of hydrotherapy in rheumatoid arthritis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 9, 206-215.
- HALLS, S., LAW, R. J., JONES, J. G., MARKLAND, D. A., MADDISON, P. J. & THOM, J. M. 2017. Health professionals' perceptions of the effects of exercise on joint health in rheumatoid arthritis patients. *Musculoskeletal care*, 15, 196-209.
- HAMMAM, N., EZEUGWU, V. E., RUMSEY, D. G., MANNS, P. J. & PRITCHARD-WIART, L. 2019. Physical activity, sedentary behavior, and long-term cardiovascular risk in individuals with rheumatoid arthritis. *The Physician and Sportsmedicine*, 47, 463-470.
- HAMNER, J. W., TAN, C. O., TZENG, Y. C. & TAYLOR, J. A. 2012. Cholinergic control of the cerebral vasculature in humans. *J Physiol*, 590, 6343-52.
- HANSFORD, H. J., WEWEGE, M. A., CASHIN, A. G., HAGSTROM, A. D., CLIFFORD, B. K., MCAULEY, J. H. & JONES, M. D. 2022. If exercise is medicine, why don't we know the dose? An overview of systematic reviews assessing reporting quality of exercise interventions in health and disease. *British journal of sports medicine*, 56, 692-700.
- HARWOOD, A. E., RUSSELL, S., OKWOSE, N. C., MCGUIRE, S., JAKOVLJEVIC, D. G. & MCGREGOR, G. 2021. A systematic review of rehabilitation in chronic heart failure: evaluating the reporting of exercise interventions. *ESC heart failure*, 8, 3458-3471.
- HEASLIP, V., THOMPSON, R., TAURINGANA, M., HOLLAND, S. & GLENDENING, N. 2022. Health inequity in the UK: exploring health inequality and inequity. *Practice Nursing*, 33, 72-76.
- HENCHOZ, Y., ZUFFEREY, P. & SO, A. 2013. Stages of change, barriers, benefits, and preferences for exercise in RA patients: a cross-sectional study. *Scandinavian journal of rheumatology*, 42, 136-145.
- HERNÁNDEZ-HERNÁNDEZ, M. V. & DÍAZ-GONZÁLEZ, F. 2017. Role of physical activity in the management and assessment of rheumatoid arthritis patients. *Reumatología Clínica (English Edition)*, 13, 214-220.
- HERNANDEZ-HERNANDEZ, V., FERRAZ-AMARO, I. & DÍAZ-GONZÁLEZ, F. 2014. Influence of disease activity on the physical activity of rheumatoid arthritis patients. *Rheumatology*, 53, 722-731.
- HESKETH, K., JONES, H., KINNAFICK, F., SHEPHERD, S. O., WAGENMAKERS, A. J., STRAUSS, J. A. & COCKS, M. 2021a. Home-Based HIIT and Traditional MICT Prescriptions Improve Cardiorespiratory Fitness to a Similar Extent Within an Exercise Referral Scheme for At-Risk Individuals. *Frontiers in physiology*, 2015.
- HESKETH, K., JONES, H., KINNAFICK, F., SHEPHERD, S. O., WAGENMAKERS, A. J. M., STRAUSS, J. A. & COCKS, M. 2021b. Home-Based HIIT and Traditional MICT Prescriptions Improve Cardiorespiratory Fitness to a Similar Extent Within an

- Exercise Referral Scheme for At-Risk Individuals. *Frontiers in physiology* [Online], 12. [Accessed 2021].
- HESKETH, K., LOW, J., ANDREWS, R., JONES, C. A., JONES, H., JUNG, M. E., LITTLE, J., MATEUS, C., PULSFORD, R. & SINGER, J. 2021c. Mobile Health Biometrics to Enhance Exercise and Physical Activity Adherence in Type 2 Diabetes (MOTIVATE-T2D): protocol for a feasibility randomised controlled trial. *BMJ open*, 11, e052563.
- HILDEBRAND, M., HANSEN, B. H., VAN HEES, V. T. & EKELOUND, U. 2017. Evaluation of raw acceleration sedentary thresholds in children and adults. *Scandinavian journal of medicine & science in sports*, 27, 1814-1823.
- HILDEBRAND, M., VT, V. H., HANSEN, B. H. & EKELOUND, U. 2014. Age group comparability of raw accelerometer output from wrist-and hip-worn monitors. *Medicine and science in sports and exercise*, 46, 1816-1824.
- HIPPOCRATES, R. ca 400 BC.
- HITCHON, C. A., BOIRE, G., HARAOU, B., KEYSTONE, E., POPE, J., JAMAL, S., TIN, D., THORNE, C., BYKERK, V. P. & INVESTIGATORS, C. 2016. Self-reported comorbidity is common in early inflammatory arthritis and associated with poorer function and worse arthritis disease outcomes: results from the Canadian Early Arthritis Cohort. *Rheumatology*, 55, 1751-1762.
- HODKINSON, A., KONTOPANTELIS, E., ADENIJI, C., VAN MARWIJK, H., MCMILLIAN, B., BOWER, P. & PANAGIOTI, M. 2021. Interventions Using Wearable Physical Activity Trackers Among Adults With Cardiometabolic Conditions: A Systematic Review and Meta-analysis. *JAMA Network Open*, 4, e2116382-e2116382.
- HOFFMANN, T. C., ERUETI, C. & GLASZIOU, P. P. 2013. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *Bmj*, 347.
- HOFFMANN, T. C., GLASZIOU, P. P., BOUTRON, I., MILNE, R., PERERA, R., MOHER, D., ALTMAN, D. G., BARBOUR, V., MACDONALD, H., JOHNSTON, M., LAMB, S. E., DIXON-WOODS, M., MCCULLOCH, P., WYATT, J. C., CHAN, A.-W. & MICHIE, S. 2014. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ : British Medical Journal*, 348, g1687.
- HOILAND, R. L., SMITH, K. J., CARTER, H. H., LEWIS, N. C., TYMKO, M. M., WILDFONG, K. W., BAIN, A. R., GREEN, D. J. & AINSLIE, P. N. 2017. Shear-mediated dilation of the internal carotid artery occurs independent of hypercapnia. *American Journal of Physiology-Heart and Circulatory Physiology*, 313, H24-H31.
- HOLMQVIST, M., GRÄNSMARK, E., MANTEL, Ä., ALFREDSSON, L., JACOBSSON, L. T., WALLBERG-JONSSON, S. & ASKLING, J. 2013. Occurrence and relative risk of stroke in incident and prevalent contemporary rheumatoid arthritis. *Annals of the rheumatic diseases*, 72, 541-546.
- HU, K., PENG, C. K., CZOSNYKA, M., ZHAO, P. & NOVAK, V. 2008. Nonlinear assessment of cerebral autoregulation from spontaneous blood pressure and cerebral blood flow fluctuations. *Cardiovasc Eng*, 8, 60-71.
- HUPIN, D., ROCHE, F., GREMEAUX, V., CHATARD, J.-C., ORIOL, M., GASPOZ, J.-M., BARTHÉLÉMY, J.-C. & EDOUARD, P. 2015. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged ≥ 60 years: a systematic review and meta-analysis. *British journal of sports medicine*.
- HURKMANS, E., MAES, S., DE GUCHT, V., KNITTLE, K., PEETERS, A., RONDAY, H. & VLIELAND, T. V. 2010. Motivation as a determinant of physical activity in patients with rheumatoid arthritis. *Arthritis care & research*, 62, 371-377.

- INABA, Y., CHEN, J. A. & BERGMANN, S. R. 2010. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *The International Journal of Cardiovascular Imaging*, 26, 631-640.
- INSTITUTE FOR GOVERNMENT 2021. Timeline of UK government coronavirus lockdowns and restrictions. The Institute for Government.
- INTHARAKHAM, K., BEISHON, L., PANERAI, R. B., HAUNTON, V. J. & ROBINSON, T. G. 2019. Assessment of cerebral autoregulation in stroke: a systematic review and meta-analysis of studies at rest. *Journal of Cerebral Blood Flow & Metabolism*, 39, 2105-2116.
- ISAACS, J. D. 2010. The changing face of rheumatoid arthritis: sustained remission for all? *Nature Reviews Immunology*, 10, 605-611.
- ISHIKAWA, Y. & TERAOKA, C. 2020. The impact of cigarette smoking on risk of rheumatoid arthritis: a narrative review. *Cells*, 9, 475.
- JACKSON, A. S., BLAIR, S. N., MAHAR, M. T., WIER, L. T., ROSS, R. M. & STUTEVILLE, J. E. 1990. Prediction of functional aerobic capacity without exercise testing. *Medicine and science in sports and exercise*, 22, 863-870.
- JAGPAL, A. & NAVARRO-MILLÁN, I. 2018. Cardiovascular co-morbidity in patients with rheumatoid arthritis: a narrative review of risk factors, cardiovascular risk assessment and treatment. *BMC rheumatology*, 2, 1-14.
- JIN, J., LI, J., GAN, Y., LIU, J., ZHAO, X., CHEN, J., ZHANG, R., ZHONG, Y., CHEN, X. & WU, L. 2021. Red meat intake is associated with early onset of rheumatoid arthritis: a cross-sectional study. *Scientific reports*, 11, 5681.
- JIVOFF, L. 1975. Rehabilitation and rheumatoid arthritis. *Bulletin on the rheumatic diseases*, 26, 838.
- JOHN, H., KITAS, G., TOMS, T. & GOODSON, N. 2009. Cardiovascular co-morbidity in early rheumatoid arthritis. *Best Practice & Research Clinical Rheumatology*, 23, 71-82.
- JOHNSON, T. M., YANG, Y., ROUL, P., SAUER, B. C., CANNON, G. W., KUNKEL, G., MICHAUD, K., BAKER, J. F., MIKULS, T. R. & ENGLAND, B. R. 2023. A Narrowing Mortality Gap: Temporal Trends of Cause - Specific Mortality in a National Matched Cohort Study in US Veterans With Rheumatoid Arthritis. *Arthritis Care & Research*, 75, 1648-1658.
- JUNG, M., LOCKE, S., BOURNE, J., BEAUCHAMP, M., LEE, T., SINGER, J., MACPHERSON, M., BARRY, J., JONES, C. & LITTLE, J. 2020a. Cardiorespiratory fitness and accelerometer-determined physical activity following one year of free-living high-intensity interval training and moderate-intensity continuous training: a randomized trial. *International Journal of Behavioral Nutrition and Physical Activity*, 17, 1-10.
- JUNG, M. E., LOCKE, S. R., BOURNE, J. E., BEAUCHAMP, M. R., LEE, T., SINGER, J., MACPHERSON, M., BARRY, J., JONES, C. & LITTLE, J. P. 2020b. Cardiorespiratory fitness and accelerometer-determined physical activity following one year of free-living high-intensity interval training and moderate-intensity continuous training: a randomized trial. *International Journal of Behavioral Nutrition and Physical Activity*, 17, 25.
- KARPOUZAS, G. A., MALPESO, J., CHOI, T.-Y., LI, D., MUNOZ, S. & BUDOFF, M. J. 2014. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. *Annals of the Rheumatic Diseases*, 73, 1797-1804.
- KATZ, P., ANDONIAN, B. J. & HUFFMAN, K. M. 2020. Benefits and promotion of physical activity in rheumatoid arthritis. *Current opinion in rheumatology*, 32, 307-314.

- KATZ, P., MARGARETTEN, M., GREGORICH, S. & TRUPIN, L. 2018. Physical activity to reduce fatigue in rheumatoid arthritis: a randomized controlled trial. *Arthritis care & research*, 70, 1-10.
- KELLEY, G. A. & KELLEY, K. S. 2014. Effects of exercise on depressive symptoms in adults with arthritis and other rheumatic disease: a systematic review of meta-analyses. *BMC Musculoskeletal Disorders*, 15, 1-9.
- KHAYLIS, A., YIASLAS, T., BERGSTROM, J. & GORE-FELTON, C. 2010. A review of efficacious technology-based weight-loss interventions: five key components. *Telemedicine and e-Health*, 16, 931-938.
- KIM, J.-W. & SUH, C.-H. 2020. Systemic manifestations and complications in patients with rheumatoid arthritis. MDPI.
- KING, A. C., HEKLER, E. B., GRIECO, L. A., WINTER, S. J., SHEATS, J. L., BUMAN, M. P., BANERJEE, B., ROBINSON, T. N. & CIRIMELE, J. 2016. Effects of three motivationally targeted mobile device applications on initial physical activity and sedentary behavior change in midlife and older adults: a randomized trial. *PloS one*, 11, e0156370.
- KING, A. C., TAYLOR, C. B., HASKELL, W. L. & DEBUSK, R. F. 1990. Identifying strategies for increasing employee physical activity levels: Findings from the Stanford/Lockheed exercise survey. *Health Education Quarterly*, 17, 269-285.
- KINNAFICK, F.-E., THØGERSEN-NTOUMANI, C., SHEPHERD, S. O., WILSON, O. J., WAGENMAKERS, A. J. & SHAW, C. S. 2018. In it together: a qualitative evaluation of participant experiences of a 10-week, group-based, workplace HIIT program for insufficiently active adults. *Journal of Sport and Exercise Psychology*, 40, 10-19.
- KIS, O., BUCH, A., STERN, N. & MORAN, D. S. 2019. Minimally supervised home-based resistance training and muscle function in older adults: A meta-analysis. *Archives of gerontology and geriatrics*, 84, 103909.
- KITAS, G. D. & GABRIEL, S. E. 2011. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. *Annals of the Rheumatic Diseases*, 70, 8.
- KLEPIN, K., WING, D., HIGGINS, M., NICHOLS, J. & GODINO, J. G. 2019. Validity of cardiorespiratory fitness measured with fitbit compared to V̇O₂max. *Medicine and Science in Sports and Exercise*, 51, 2251.
- KNITTLE, K., DE GUCHT, V., HURKMANS, E., PEETERS, A., RONDAY, K., MAES, S. & VLIELAND, T. V. 2015. Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial. *Clinical rheumatology*, 34, 231-238.
- KOBAYASHI, S., MOMOHARA, S., KAMATANI, N. & OKAMOTO, H. 2008. Molecular aspects of rheumatoid arthritis: role of environmental factors. *The FEBS journal*, 275, 4456-4462.
- KOBIYAMA, K. & LEY, K. 2018. Atherosclerosis: a chronic inflammatory disease with an autoimmune component. *Circulation research*, 123, 1118-1120.
- KOEP, J. L., WESTON, M. E., BARKER, A. R., BAILEY, T. G., COOMBES, J. S., LESTER, A. & BOND, B. 2022. The within - and between - day reliability of cerebrovascular reactivity using traditional and novel analytical approaches. *Experimental Physiology*, 107, 29-41.
- KOHL, H. W., CRAIG, C. L., LAMBERT, E. V., INOUE, S., ALKANDARI, J. R., LEETONGIN, G. & KAHLMEIER, S. 2012. The pandemic of physical inactivity: global action for public health. *The Lancet*, 380, 294-305.
- KOLLER, A. & TOTH, P. 2012. Contribution of flow-dependent vasomotor mechanisms to the autoregulation of cerebral blood flow. *Journal of vascular research*, 49, 375-389.

- KOOIMAN, T. J., DONTJE, M. L., SPRENGER, S. R., KRIJNEN, W. P., VAN DER SCHANS, C. P. & DE GROOT, M. 2015. Reliability and validity of ten consumer activity trackers. *BMC sports science, medicine and rehabilitation*, 7, 1-11.
- KROENKE, K., STRINE, T. W., SPITZER, R. L., WILLIAMS, J. B., BERRY, J. T. & MOKDAD, A. H. 2009. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*, 114, 163-73.
- KUSHI, L. H., KAYE, S. A., FOLSOM, A. R., SOLER, J. T. & PRINEAS, R. J. 1988. Accuracy and reliability of self-measurement of body girths. *American Journal of Epidemiology*, 128, 740-748.
- LABRECQUE, L., DRAPEAU, A., RAHIMALY, K., IMHOFF, S. & BRASSARD, P. 2021. Dynamic cerebral autoregulation and cerebrovascular carbon dioxide reactivity in middle and posterior cerebral arteries in young endurance-trained women. *Journal of Applied Physiology*, 130, 1724-1735.
- LABRECQUE, L., RAHIMALY, K., IMHOFF, S., PAQUETTE, M., LE BLANC, O., MALENFANT, S., DRAPEAU, A., SMIRL, J. D., BAILEY, D. M. & BRASSARD, P. 2019. Dynamic cerebral autoregulation is attenuated in young fit women. *Physiological Reports*, 7, e13984.
- LACROIX, A., HORTOBAGYI, T., BEURSKENS, R. & GRANACHER, U. 2017. Effects of supervised vs. unsupervised training programs on balance and muscle strength in older adults: a systematic review and meta-analysis. *Sports medicine*, 47, 2341-2361.
- LANDIS, J. R. & KOCH, G. G. 1977. The measurement of observer agreement for categorical data. *biometrics*, 159-174.
- LARANJO, L., DING, D., HELENO, B., KOCABALLI, B., QUIROZ, J. C., TONG, H. L., CHAHWAN, B., NEVES, A. L., GABARRON, E., DAO, K. P., RODRIGUES, D., NEVES, G. C., ANTUNES, M. L., COIERA, E. & BATES, D. W. 2021. Do smartphone applications and activity trackers increase physical activity in adults? Systematic review, meta-analysis and metaregression. *British Journal of Sports Medicine*, 55, 422.
- LARKIN, L., KENNEDY, N. & GALLAGHER, S. 2015. Promoting physical activity in rheumatoid arthritis: a narrative review of behaviour change theories. *Disability and rehabilitation*, 37, 2359-2366.
- LARSEN, R. T., CHRISTENSEN, J., JUHL, C. B., ANDERSEN, H. B. & LANGBERG, H. 2019. Physical activity monitors to enhance amount of physical activity in older adults—a systematic review and meta-analysis. *European Review of Aging and Physical Activity*, 16, 1-13.
- LARSSON, M., STEENBERGEN, W. & STROMBERG, T. 2002. Influence of optical properties and fiber separation on laser Doppler flowmetry. *Journal of Biomedical Optics*, 7, 236-243.
- LASSEN, N. A. 1959. Cerebral Blood Flow and Oxygen Consumption in Man. *Physiological Reviews*, 39, 183-238.
- LASSERE, M., RAPPO, J., PORTEK, I., STURGESS, A. & EDMONDS, J. 2013. How many life years are lost in patients with rheumatoid arthritis? Secular cause - specific and all - cause mortality in rheumatoid arthritis, and their predictors in a long - term Australian cohort study. *Internal medicine journal*, 43, 66-72.
- LAVI, S., EGBARYA, R., LAVI, R. & JACOB, G. 2003. Role of nitric oxide in the regulation of cerebral blood flow in humans: chemoregulation versus mechanoregulation. *Circulation*, 107, 1901-1905.
- LAW, R. J., MARKLAND, D. A., JONES, J. G., MADDISON, P. J. & THOM, J. M. 2013. Perceptions of issues relating to exercise and joint health in rheumatoid arthritis: a UK - based questionnaire study. *Musculoskeletal Care*, 11, 147-158.

- LEE, D.-C., ARTERO, E. G., SUI, X. & BLAIR, S. N. 2010. Mortality trends in the general population: the importance of cardiorespiratory fitness. *Journal of psychopharmacology*, 24, 27-35.
- LEE, I. M., SHIROMA, E. J., LOBELO, F., PUSKA, P., BLAIR, S. N. & KATZMARZYK, P. T. 2012a. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *The Lancet*, 380, 219-229.
- LEE, J., DUNLOP, D., EHRLICH-JONES, L., SEMANIK, P., SONG, J., MANHEIM, L. & CHANG, R. W. 2012b. Public health impact of risk factors for physical inactivity in adults with rheumatoid arthritis. *Arthritis Care & Research*, 64, 488-493.
- LEEB, B. F., HAINDL, P. M., MAKTARI, A., NOTHNAGL, T. & RINTELEN, B. 2008. Patient-centered rheumatoid arthritis disease activity assessment by a modified RADAI. *The Journal of Rheumatology*, 35, 1294-1299.
- LEMMEY, A. B., MARCORA, S. M., CHESTER, K., WILSON, S., CASANOVA, F. & MADDISON, P. J. 2009. Effects of high - intensity resistance training in patients with rheumatoid arthritis: A randomized controlled trial. *Arthritis Care & Research*, 61, 1726-1734.
- LEVICK, J. R. 2013. *An introduction to cardiovascular physiology*, Butterworth-Heinemann.
- LEWIS, N., GELINAS, J. C., AINSLIE, P. N., SMIRL, J. D., AGAR, G., MELZER, B., ROLF, J. D. & EVES, N. D. 2019. Cerebrovascular function in patients with chronic obstructive pulmonary disease: the impact of exercise training. *American Journal of Physiology-Heart and Circulatory Physiology*, 316, H380-H391.
- LIAO, K. P. & SOLOMON, D. H. 2013. Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. *Rheumatology*, 52, 45-52.
- LIBBY, P. 2008. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. *The American journal of medicine*, 121, S21-S31.
- LINDHARDSEN, J., AHLEHOFF, O., GISLASON, G. H., MADSEN, O. R., OLESEN, J. B., SVENDSEN, J. H., TORP-PEDERSEN, C. & HANSEN, P. R. 2012. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *Bmj*, 344.
- LINN-RASKER, S. P., VAN DER HELM-VAN, A. H., VAN GAALEN, F. A., KLOPPENBURG, M., DE VRIES, R., LE CESSIE, S., BREEDVELD, F. C., TOES, R. E. & HUIZINGA, T. W. 2005. Smoking is a risk factor for anti-CCP antibodies only in RA patients that carry HLA-DRB1 shared epitope alleles. *Annals of the rheumatic diseases*.
- LIPSITZ, L. A., MUKAI, S., HAMNER, J., GAGNON, M. & BABIKIAN, V. 2000. Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. *Stroke*, 31, 1897-1903.
- LOBELO, F., ROHM YOUNG, D., SALLIS, R., GARBER, M. D., BILLINGER, S. A., DUPERLY, J., HUTBER, A., PATE, R. R., THOMAS, R. J. & WIDLANSKY, M. E. 2018. Routine assessment and promotion of physical activity in healthcare settings: a scientific statement from the American Heart Association. *Circulation*, 137, e495-e522.
- LOPES, S., DINIZ, F., MESQUITA BASTOS, J., OLIVEIRA, J., POLÓNIA, J., ALVES, A. J., RIBEIRO, F. & FIGUEIREDO, D. 2023. "What do we think?": a qualitative exploratory study of acceptability and experiences of individuals with resistant hypertension after completing a physical exercise program (the EnRICH trial). *Disability and Rehabilitation*, 1-8.
- LUCAS, S. J. E., TZENG, Y. C., GALVIN, S. D., THOMAS, K. N., OGOH, S. & AINSLIE, P. N. 2010. Influence of Changes in Blood Pressure on Cerebral Perfusion and Oxygenation. *Hypertension*, 55, 698-705.

- LWIN, M. N., SERHAL, L., HOLROYD, C. & EDWARDS, C. J. 2020. Rheumatoid arthritis: the impact of mental health on disease: a narrative review. *Rheumatology and therapy*, 7, 457-471.
- MACINTOSH, B. R., MURIAS, J. M., KEIR, D. A. & WEIR, J. M. 2021. What is moderate to vigorous exercise intensity? *Frontiers in Physiology*, 1481.
- MANNING, V. L., HURLEY, M. V., SCOTT, D. L. & BEARNE, L. M. 2012. Are patients meeting the updated physical activity guidelines? Physical activity participation, recommendation, and preferences among inner-city adults with rheumatic diseases. *JCR: Journal of Clinical Rheumatology*, 18, 399-404.
- MANZI, S. & WASKO, M. C. M. 2000. Inflammation-mediated rheumatic diseases and atherosclerosis. *Annals of the rheumatic diseases*, 59, 321-325.
- MARÍN, J. S., MAZENETT-GRANADOS, E. A., SALAZAR-URIBE, J. C., SARMIENTO, M., SUÁREZ, J. F., ROJAS, M., MUNERA, M., PÉREZ, R., MORALES, C. & DOMINGUEZ, J. I. 2023. Increased incidence of rheumatoid arthritis after COVID-19. *Autoimmunity Reviews*, 103409.
- MARKUS, H. & CULLINANE, M. 2001. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. *Brain*, 124, 457-467.
- MASUKO, K. 2014. Rheumatoid cachexia revisited: a metabolic co-morbidity in rheumatoid arthritis. *Frontiers in nutrition*, 1, 20.
- MATCHAM, F., SCOTT, I. C., RAYNER, L., HOTOPF, M., KINGSLEY, G. H., NORTON, S., SCOTT, D. L. & STEER, S. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Seminars in arthritis and rheumatism*, 2014. Elsevier, 123-130.
- MATEO, G. F., GRANADO-FONT, E., FERRÉ-GRAU, C. & MONTAÑA-CARRERAS, X. 2015. Mobile phone apps to promote weight loss and increase physical activity: a systematic review and meta-analysis. *Journal of medical Internet research*, 17, e4836.
- MATTHEW, C. E. 2005. Calibration of accelerometer output for adults. *Medicine and science in sports and exercise*, 37, S512-22.
- MAXWELL, J. D., BANNELL, D. J., BRISLANE, A., CARTER, S. E., MILLER, G. D., ROBERTS, K. A., HOPKINS, N. D., LOW, D. A., CARTER, H. H. & THOMPSON, A. 2022. The impact of age, sex, cardio-respiratory fitness, and cardiovascular disease risk on dynamic cerebral autoregulation and baroreflex sensitivity. *European Journal of Applied Physiology*, 122, 1531-1541.
- MAXWELL, J. D., FRANCE, M., FINNIGAN, L. E. M., CARTER, H. H., THIJSEN, D. H. J. & JONES, H. 2021. Can exercise training enhance the repeated remote ischaemic preconditioning stimulus on peripheral and cerebrovascular function in high-risk individuals? *European Journal of Applied Physiology*, 121, 1167-1178.
- MAYOUX-BENHAMOU, A., GIRAUDET-LE QUINTREC, J.-S., RAVAUD, P., CHAMPION, K., DERNIS, E., ZERKAK, D., ROY, C., KAHAN, A., REVEL, M. & DOUGADOS, M. 2008. Influence of patient education on exercise compliance in rheumatoid arthritis: a prospective 12-month randomized controlled trial. *The Journal of rheumatology*, 35, 216-223.
- MCDERMOTT, M. M. & NEWMAN, A. B. 2021. Remote research and clinical trial integrity during and after the coronavirus pandemic. *Jama*, 325, 1935-1936.
- MCINNES, I. B. & SCHETT, G. 2011. The pathogenesis of rheumatoid arthritis. *New England Journal of Medicine*, 365, 2205-2219.

- MCKENNA, S., KELLY, G. & KENNEDY, N. 2019. A survey of physiotherapists' current management and the promotion of physical activity, in people with rheumatoid arthritis. *Disability and Rehabilitation*, 41, 2183-2191.
- MENDES, R., SOUSA, N., ALMEIDA, A., SUBTIL, P., GUEDES-MARQUES, F., REIS, V. M. & THEMUDO-BARATA, J. L. 2016. Exercise prescription for patients with type 2 diabetes—a synthesis of international recommendations: narrative review. *British journal of sports medicine*, 50, 1379-1381.
- METSIOS, G. S. & KITAS, G. D. 2018. Physical activity, exercise and rheumatoid arthritis: effectiveness, mechanisms and implementation. *Best practice & research Clinical rheumatology*, 32, 669-682.
- METSIOS, G. S. & LEMMEY, A. 2015. Exercise as Medicine in Rheumatoid Arthritis: Effects on Function, Body Composition, and Cardiovascular Disease Risk. *Journal of Clinical Exercise Physiology*, 4, 14-22.
- METSIOS, G. S., MOE, R. H., VAN DER ESCH, M., VAN ZANTEN, J., FENTON, S. A. M., KOUTEDAKIS, Y., VITALIS, P., KENNEDY, N., BRODIN, N., BOSTROM, C., SWINNEN, T. W., TZIKA, K., NIEDERMANN, K., NIKIPHOROU, E., FRAGOULIS, G. E., VLIELAND, T., VAN DEN ENDE, C. H. M. & KITAS, G. D. 2020. The effects of exercise on cardiovascular disease risk factors and cardiovascular physiology in rheumatoid arthritis. *Rheumatol Int*, 40, 347-357.
- METSIOS, G. S., STAVROPOULOS-KALINOGLU, A., PANOULAS, V. F., WILSON, M., NEVILL, A. M., KOUTEDAKIS, Y. & KITAS, G. D. 2009. Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. *European Journal of Preventive Cardiology*, 16, 188-194.
- METSIOS, G. S., STAVROPOULOS-KALINOGLU, A., SANDOO, A., VAN ZANTEN, J. J. V., TOMS, T. E., JOHN, H. & KITAS, G. D. 2010. Vascular function and inflammation in rheumatoid arthritis: the role of physical activity. *The open cardiovascular medicine journal*, 4, 89.
- METSIOS, G. S., STAVROPOULOS-KALINOGLU, A., VAN ZANTEN, J. J. V., NIGHTINGALE, P., SANDOO, A., DIMITROULAS, T., KITAS, G. D. & KOUTEDAKIS, Y. 2013. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. *Annals of the rheumatic diseases*, annrheumdis-2013-203291.
- METSIOS, G. S., STAVROPOULOS-KALINOGLU, A., VAN ZANTEN, J. J. V., NIGHTINGALE, P., SANDOO, A., DIMITROULAS, T., KITAS, G. D. & KOUTEDAKIS, Y. 2014. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. *Annals of the rheumatic diseases*, 73, 748-751.
- MEYER, J., MCDOWELL, C., LANSING, J., BROWER, C., SMITH, L., TULLY, M. & HERRING, M. 2020. Changes in Physical Activity and Sedentary Behavior in Response to COVID-19 and Their Associations with Mental Health in 3052 US Adults. *Int J Environ Res Public Health*, 17.
- MICHIE, S., ABRAHAM, C., WHITTINGTON, C., MCATEER, J. & GUPTA, S. 2009. Effective techniques in healthy eating and physical activity interventions: a meta-regression. *Health Psychol*, 28, 690-701.
- MICHIE, S., VAN STRALEN, M. M. & WEST, R. 2011. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science*, 6, 42.
- MILLER, F. L., O'CONNOR, D. P., HERRING, M. P., SAILORS, M. H., JACKSON, A. S., DISHMAN, R. K. & BRAY, M. S. 2014. Exercise dose, exercise adherence, and associated health outcomes in the TIGER study. *Medicine and science in sports and exercise*, 46.

- MILLER, K. B., HOWERY, A. J., RIVERA-RIVERA, L. A., JOHNSON, S. C., ROWLEY, H. A., WIEBEN, O. & BARNES, J. N. 2019. Age-related reductions in cerebrovascular reactivity using 4D flow MRI. *Frontiers in aging neuroscience*, 11, 281.
- MINISTRY OF HOUSING COMMUNITIES & LOCAL GOVERNMENT 2015. MINISTRY OF HOUSING COMMUNITIES & LOCAL GOVERNMENT. 2015. English Indices of Deprivation 2015 [Online]. Government Official Statistics,. Available: <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015>
- MISHRA, P., PANDEY, C. M., SINGH, U., GUPTA, A., SAHU, C. & KESHRI, A. 2019. Descriptive statistics and normality tests for statistical data. *Annals of cardiac anaesthesia*, 22, 67.
- MONCHER, F. J. & PRINZ, R. J. 1991. Treatment fidelity in outcome studies. *Clinical psychology review*, 11, 247-266.
- MORGAN, F., BATTERSBY, A., WEIGHTMAN, A. L., SEARCHFIELD, L., TURLEY, R., MORGAN, H., JAGROO, J. & ELLIS, S. 2016a. Adherence to exercise referral schemes by participants – what do providers and commissioners need to know? A systematic review of barriers and facilitators. *BMC Public Health*, 16, 227.
- MORGAN, F., BATTERSBY, A., WEIGHTMAN, A. L., SEARCHFIELD, L., TURLEY, R., MORGAN, H., JAGROO, J. & ELLIS, S. 2016b. Adherence to exercise referral schemes by participants—what do providers and commissioners need to know? A systematic review of barriers and facilitators. *BMC public health*, 16, 1-11.
- MORGAN, O. 2005. Approaches to increase physical activity: reviewing the evidence for exercise-referral schemes. *Public Health*, 119, 361-370.
- MORRIS, J. N., HEADY, J. A., RAFFLE, P. A. B., ROBERTS, C. G. & PARKS, J. W. 1953. CORONARY HEART-DISEASE AND PHYSICAL ACTIVITY OF WORK. *The Lancet*, 262, 1111-1120.
- MOSS, R. J., SÜLE, A. & KOHL, S. 2019. eHealth and mHealth. *European Journal of Hospital Pharmacy*, 26, 57.
- NACI, H. & IOANNIDIS, J. P. 2013. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *Bmj*, 347, f5577.
- NADAREISHVILI, Z., MICHAUD, K., HALLENBECK, J. M. & WOLFE, F. 2008. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case–control study. *Arthritis Care & Research*, 59, 1090-1096.
- NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE 2014. Physical Activity: Exercise Referral Schemes (PH54). *London, UK*.
- NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE 2018a. Evidence Standards Framework for Digital Health Technologies.
- NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE. 2018b. *Rheumatoid arthritis in adults: management (NICE guideline NG100)* [Online]. Available: <https://www.nice.org.uk/guidance/ng100> [Accessed].
- NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE 2018c. Surveillance of Physical Activity: Exercise Referral Schemes (NICE Guideline PH54). *London, UK*.
- NES, B. M., GUTVIK, C. R., LAVIE, C. J., NAUMAN, J. & WISLØFF, U. 2017. Personalized activity intelligence (PAI) for prevention of cardiovascular disease and promotion of physical activity. *The American journal of medicine*, 130, 328-336.
- NEUBERGER, G. B., AARONSON, L. S., GAJEWSKI, B., EMBRETSON, S. E., CAGLE, P. E., LOUDON, J. K. & MILLER, P. A. 2007. Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. *Arthritis Care & Research*, 57, 943-952.
- NHS ENGLAND 2019. The NHS Long Term Plan.

- NILSSON, G. E., TENLAND, T. & OBERG, P. A. 1980. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. *IEEE Transactions on Biomedical Engineering*, 597-604.
- NOONAN, D. & SIMMONS, L. A. 2021. Navigating nonessential research trials during COVID19: the push we needed for using digital technology to increase access for rural participants? *The Journal of rural health: official journal of the American Rural Health Association and the National Rural Health Care Association*, 37, 185.
- NOVAK, V., NOVAK, P., SPIES, J. M. & LOW, P. A. 1998. Autoregulation of Cerebral Blood Flow in Orthostatic Hypotension. *Stroke*, 29, 104-111.
- NUMAN, T., BAIN, A. R., HOILAND, R. L., SMIRL, J. D., LEWIS, N. C. & AINSLIE, P. N. 2014. Static autoregulation in humans: a review and reanalysis. *Medical Engineering & Physics*, 36, 1487-1495.
- O'LEARY, D. H., POLAK, J. F., KRONMAL, R. A., MANOLIO, T. A., BURKE, G. L. & WOLFSON JR, S. K. 1999. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *New England Journal of Medicine*, 340, 14-22.
- O'DWYER, T., RAFFERTY, T., O'SHEA, F., GISSANE, C. & WILSON, F. 2014. Physical activity guidelines: is the message getting through to adults with rheumatic conditions? *Rheumatology*, 53, 1812-1817.
- OGAWA, Y., IWASAKI, K., AOKI, K., GOKAN, D., HIROSE, N., KATO, J. & OGAWA, S. 2010. The different effects of midazolam and propofol sedation on dynamic cerebral autoregulation. *Anesth Analg*, 111, 1279-84.
- OSTHOFF, A.-K. R., NIEDERMANN, K., BRAUN, J., ADAMS, J., BRODIN, N., DAGFINRUD, H., DURUOZ, T., ESBENSEN, B. A., GÜNTHER, K.-P. & HURKMANS, E. 2018. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Annals of the rheumatic diseases*, 77, 1251-1260.
- PALAZZO, C., KLINGER, E., DORNER, V., KADRI, A., THIERRY, O., BOUMENIR, Y., MARTIN, W., POIRAUDEAU, S. & VILLE, I. 2016. Barriers to home-based exercise program adherence with chronic low back pain: Patient expectations regarding new technologies. *Annals of Physical and Rehabilitation Medicine*, 59, 107-113.
- PANERAI, R. B., BRASSARD, P., BURMA, J. S., CASTRO, P., CLAASSEN, J. A., VAN LIESHOUT, J. J., LIU, J., LUCAS, S. J., MINHAS, J. S. & MITSIS, G. D. 2023. Transfer function analysis of dynamic cerebral autoregulation: A CARNet white paper 2022 update. *Journal of Cerebral Blood Flow & Metabolism*, 43, 3-25.
- PANOULAS, V. F., METSIOS, G. S., PACE, A., JOHN, H., TREHARNE, G., BANKS, M. & KITAS, G. D. 2008. Hypertension in rheumatoid arthritis. *Rheumatology*, 47, 1286-1298.
- PARAVIDINO, V. B., MEDIANO, M. F. F., CROCHEMORE-SILVA, I., DA CRUZ, V. L., ANTUNES, M. M. L., BEAULIEU, K., GIBBONS, C., FINLAYSON, G., BLUNDELL, J. E. & SICHIERI, R. 2021. The compensatory effect of exercise on physical activity and energy intake in young men with overweight: The EFACT randomised controlled trial. *Physiology & Behavior*, 229, 113249.
- PARK, Y. B., LEE, S. K., LEE, W. K., SUH, C. H., LEE, C. W., LEE, C. H., SONG, C. H. & LEE, J. 1999. Lipid profiles in untreated patients with rheumatoid arthritis. *The Journal of rheumatology*, 26, 1701-1704.
- PASCERI, V. & YE, E. T. 1999. A tale of two diseases: atherosclerosis and rheumatoid arthritis. *Am Heart Assoc*.
- PASYK, K. A., THOMAS, S. V., HASSETT, C. A., CHERRY, G. W. & FALLER, R. 1989. Regional differences in capillary density of the normal human dermis. *Plastic and reconstructive surgery*, 83, 939-945.

- PATE, R. R., PRATT, M., BLAIR, S. N., HASKELL, W. L., MACERA, C. A., BOUCHARD, C., BUCHNER, D., ETTINGER, W., HEATH, G. W., KING, A. C., KRISKA, A., LEON, A. S., MARCUS, B. H., MORRIS, J., PAFFENBARGER, R. S., JR, PATRICK, K., POLLOCK, M. L., RIPPE, J. M., SALLIS, J. & WILMORE, J. H. 1995. Physical Activity and Public Health: A Recommendation From the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*, 273, 402-407.
- PAVEY, T., ANOKYE, N., TAYLOR, A., TRUEMAN, P., MOXHAM, T., FOX, K., HILLSDON, M., GREEN, C., CAMPBELL, J. & FOSTER, C. 2011. The clinical effectiveness and cost-effectiveness of exercise referral schemes: a systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*, 15, i.
- PAVEY, T., TAYLOR, A., HILLSDON, M., FOX, K., CAMPBELL, J., FOSTER, C., MOXHAM, T., MUTRIE, N., SEARLE, J. & TAYLOR, R. 2012. Levels and predictors of exercise referral scheme uptake and adherence: a systematic review. *Journal of Epidemiology and Community Health*, 66, 737.
- PEÇANHA, T., GOESSLER, K. F., ROSCHEL, H. & GUALANO, B. 2020. Social isolation during the COVID-19 pandemic can increase physical inactivity and the global burden of cardiovascular disease. *American Journal of Physiology-Heart and Circulatory Physiology*, 318, H1441-H1446.
- PEDERSEN, B. K. & SALTIN, B. 2006. Evidence for prescribing exercise as therapy in chronic disease. *Scandinavian journal of medicine & science in sports*, 16, 3-63.
- PEDERSEN, B. K. & SALTIN, B. 2015. Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scandinavian Journal of Medicine & Science in Sports*, 25, 1-72.
- PERETTI, A., AMENTA, F., TAYEBATI, S. K., NITTARI, G. & MAHDI, S. S. 2017. Telerehabilitation: review of the state-of-the-art and areas of application. *JMIR rehabilitation and assistive technologies*, 4, e7511.
- PÉREZ-GISBERT, L., TORRES-SÁNCHEZ, I., ORTIZ-RUBIO, A., CALVACHE-MATEO, A., LÓPEZ-LÓPEZ, L., CABRERA-MARTOS, I. & VALENZA, M. C. 2021. Effects of the COVID-19 pandemic on physical activity in chronic diseases: a systematic review and meta-analysis. *International journal of environmental research and public health*, 18, 12278.
- PERSKI, O., BLANDFORD, A., WEST, R. & MICHIE, S. 2017. Conceptualising engagement with digital behaviour change interventions: a systematic review using principles from critical interpretive synthesis. *Translational behavioral medicine*, 7, 254-267.
- PETERS, A., SCHWEIGER, U., PELLERIN, L., HUBOLD, C., OLTMANNS, K., CONRAD, M., SCHULTES, B., BORN, J. & FEHM, H. 2004. The selfish brain: competition for energy resources. *Neuroscience & Biobehavioral Reviews*, 28, 143-180.
- PETRELLI, F., MARIANI, F. M., ALUNNO, A. & PUXEDDU, I. 2022. Pathogenesis of rheumatoid arthritis: One year in review 2022. *Clin. Exp. Rheumatol*, 40, 475-482.
- PETROVSKÁ, N., PRAJZLEROVÁ, K., VENCOVSKÝ, J., ŠENOLT, L. & FILKOVÁ, M. 2021. The pre-clinical phase of rheumatoid arthritis: from risk factors to prevention of arthritis. *Autoimmunity Reviews*, 20, 102797.
- PINTO, A. J., REZENDE, D., SIECZKOWSKA, S. M., MEIRELES, K., BONFIGLIOLI, K., RIBEIRO, A. C. M., BONFÁ, E., OWEN, N., DUNSTAN, D. W., ROSCHEL, H. & GUALANO, B. 2020. Increased prolonged sitting in rheumatoid arthritis patients during the COVID-19 pandemic: a within-subjects, accelerometer-based study. *medRxiv*, 2020.09.09.20191395.
- PINTO, A. J., ROSCHEL, H., DE SÁ PINTO, A. L., LIMA, F. R., PEREIRA, R. M. R., SILVA, C. A., BONFÁ, E. & GUALANO, B. 2017. Physical inactivity and sedentary behavior:

- Overlooked risk factors in autoimmune rheumatic diseases? *Autoimmunity Reviews*, 16, 667-674.
- PIRES, P. W., RAMOS, C. M. D., MATIN, N. & DORRANCE, A. M. 2013. The effects of hypertension on the cerebral circulation. *American Journal of Physiology-Heart and Circulatory Physiology*, 304, H1598-H1614.
- PLASQUI, G. 2008. The role of physical activity in rheumatoid arthritis. *Physiology & behavior*, 94, 270-275.
- PLOW, M. & GOLDING, M. 2017. Using mHealth technology in a self-management intervention to promote physical activity among adults with chronic disabling conditions: randomized controlled trial. *JMIR mHealth and uHealth*, 5, e6394.
- POLLARD, L., CHOY, E. & SCOTT, D. 2005. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. *Clinical and experimental rheumatology*, 23, S43.
- PONS, N. C., MONTALÀ, N., VALVERDE, J., BRELL, M., FERRER, I. & MARTÍNEZ-YÉLAMOS, S. 2010. Isolated cerebral vasculitis associated with rheumatoid arthritis. *Joint Bone Spine*, 77, 361-363.
- PORTA, A., FANTINATO, A., BARI, V., GELPI, F., CAIRO, B., DE MARIA, B., BERTOLDO, E. G., FIOLO, V., CALLUS, E. & DE VINCENTIIS, C. 2020. Evaluation of the impact of surgical aortic valve replacement on short-term cardiovascular and cerebrovascular controls through spontaneous variability analysis. *PLoS One*, 15, e0243869.
- PORTEGIES, M. L., DE BRUIJN, R. F., HOFMAN, A., KOUDSTAAL, P. J. & IKRAM, M. A. 2014. Cerebral vasomotor reactivity and risk of mortality: the Rotterdam Study. *Stroke*, 45, 42-47.
- POWELL, K. E., PALUCH, A. E. & BLAIR, S. N. 2011. Physical Activity for Health: What Kind? How Much? How Intense? On Top of What? *Annual Review of Public Health*, 32, 349-365.
- PRIORESCHI, A., HODKINSON, B., AVIDON, I., TIKLY, M. & MCVEIGH, J. A. 2013. The clinical utility of accelerometry in patients with rheumatoid arthritis. *Rheumatology*, 52, 1721-1727.
- PUBLIC HEALTH ENGLAND 2014. Active E. Every day: an evidence-based approach to physical activity. .
- RADU, A.-F. & BUNGAU, S. G. 2021. Management of rheumatoid arthritis: an overview. *Cells*, 10, 2857.
- RAS, R. T., STREPPPEL, M. T., DRAIJER, R. & ZOCK, P. L. 2013. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. *International journal of cardiology*, 168, 344-351.
- REINHARD, M., MÜLLER, T., GUSCHLBAUER, B., TIMMER, J. & HETZEL, A. 2003. Transfer function analysis for clinical evaluation of dynamic cerebral autoregulation—a comparison between spontaneous and respiratory-induced oscillations. *Physiol Meas*, 24, 27-43.
- REN, Y., CHEN, Q. & LI, Z.-Y. 2015. A 3D numerical study of the collateral capacity of the circle of Willis with anatomical variation in the posterior circulation. *Biomedical engineering online*, 14, 1-12.
- REZUŞ, E., MACOVEI, L. A., BURLUI, A. M., CARDONEANU, A. & REZUŞ, C. 2021. Ischemic heart disease and rheumatoid arthritis—two conditions, the same background. *Life*, 11, 1042.
- RIDKER, P. M., HENNEKENS, C. H., BURING, J. E. & RIFAI, N. 2000. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *New England journal of medicine*, 342, 836-843.

- RITCHIE, J. & SPENCER, L. 2002. Qualitative data analysis for applied policy research. *The qualitative researcher's companion*, 573, 305-29.
- ROBERTS-THOMSON, P. J., JONES, M. E., WALKER, J. G., MACFARLANE, J. G., SMITH, M. D. & AHERN, M. J. 2002. Stochastic processes in the causation of rheumatic disease. *The Journal of Rheumatology*, 29, 2628-2634.
- RODRIGUES, R., FERRAZ, R. B., KURIMORI, C. O., GUEDES, L. K., LIMA, F. R., DE SÁ - PINTO, A. L., GUALANO, B. & ROSCHEL, H. 2020. Low - load resistance training with blood - flow restriction in relation to muscle function, mass, and functionality in women with rheumatoid arthritis. *Arthritis care & research*, 72, 787-797.
- RONGEN - VAN DARTEL, S., REPPING - WUTS, H., FLENDRIE, M., BLEIJENBERG, G., METSIOS, G., VAN DEN HOUT, W., VAN DEN ENDE, C., NEUBERGER, G., REID, A. & VAN RIEL, P. 2015. Effect of aerobic exercise training on fatigue in rheumatoid arthritis: a meta - analysis. *Arthritis care & research*, 67, 1054-1062.
- ROSS, R. 1999. Atherosclerosis—an inflammatory disease. *New England journal of medicine*, 340, 115-126.
- ROUSTIT, M. & CRACOWSKI, J.-L. 2012. Non - invasive assessment of skin microvascular function in humans: an insight into methods. *Microcirculation*, 19, 47-64.
- ROWLAND, S. P., FITZGERALD, J. E., HOLME, T., POWELL, J. & MCGREGOR, A. 2020. What is the clinical value of mHealth for patients? *NPJ digital medicine*, 3, 4.
- ROWLANDS, A., DAVIES, M., DEMPSEY, P., EDWARDSON, C., RAZIEH, C. & YATES, T. 2020. Wrist-worn accelerometers: recommending~ 1.0 mg as the minimum clinically important difference (MCID) in daily average acceleration for inactive adults. *British journal of sports medicine*.
- ROWLEY, N., STEELE, J., MANN, S., JIMENEZ, A. & HORTON, E. 2021. Delivery approaches within exercise referral schemes: a survey of current practice in England. *Journal of Physical Activity and Health*, 18, 357-373.
- ROY, M., WILLIAMS, S. M., BROWN, R. C., MEREDITH-JONES, K. A., OSBORNE, H., JOSPE, M. & TAYLOR, R. W. 2018. HIIT in the real world: outcomes from a 12-month intervention in overweight adults. *Med Sci Sports Exerc*, 50, 1818-26.
- RUBANYI, G. M. 1993. The role of endothelium in cardiovascular homeostasis and diseases. *Journal of cardiovascular pharmacology*, 22, S1-14.
- RUSSELL, M. D., GALLOWAY, J. B., ANDREWS, C. D., MACKENNA, B., GOLDACRE, B., MEHRKAR, A., CURTIS, H. J., BUTLER-COLE, B., O'DWYER, T. & QURESHI, S. 2022. Incidence and management of inflammatory arthritis in England before and during the COVID-19 pandemic: a population-level cohort study using OpenSAFELY. *The Lancet Rheumatology*, 4, e853-e863.
- SAFIRI, S., KOLAH, A. A., HOY, D., SMITH, E., BETTAMPADI, D., MANSOURNIA, M. A., ALMASI-HASHIANI, A., ASHRAFI-ASGARABAD, A., MORADI-LAKEH, M. & QORBANI, M. 2019. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017. *Annals of the rheumatic diseases*, 78, 1463-1471.
- SAINT-MAURICE, P. F., TROIANO, R. P., BASSETT, D. R., GRAUBARD, B. I., CARLSON, S. A., SHIROMA, E. J., FULTON, J. E. & MATTHEWS, C. E. 2020. Association of daily step count and step intensity with mortality among US adults. *Jama*, 323, 1151-1160.
- SAKAKURA, K., NAKANO, M., OTSUKA, F., LADICH, E., KOLODZIE, F. D. & VIRMANI, R. 2013. Pathophysiology of atherosclerosis plaque progression. *Heart, Lung and Circulation*, 22, 399-411.
- SANADA, H., HIGASHI, Y., GOTO, C., CHAYAMA, K., YOSHIZUMI, M. & SUEDA, T. 2005. Vascular function in patients with lower extremity peripheral arterial disease: a

- comparison of functions in upper and lower extremities. *Atherosclerosis*, 178, 179-185.
- SANDOO, A., CARROLL, D., METSIOS, G. S., KITAS, G. D. & VELDHUIJZEN VAN ZANTEN, J. J. 2011a. The association between microvascular and macrovascular endothelial function in patients with rheumatoid arthritis: a cross-sectional study. *Arthritis research & therapy*, 13, 1-5.
- SANDOO, A., VELDHUIJZEN VAN ZANTEN, J. J., METSIOS, G. S., CARROLL, D. & KITAS, G. D. 2011b. Vascular function and morphology in rheumatoid arthritis: a systematic review. *Rheumatology*, 50, 2125-2139.
- SANTOS, M. J., CARMONA-FERNANDES, D., CANHAO, H., CANAS DA SILVA, J., FONSECA, J. E. & GIL, V. 2012. Early vascular alterations in SLE and RA patients—a step towards understanding the associated cardiovascular risk.
- SCHUCH, F. B., VANCAMPFORT, D., FIRTH, J., ROSENBAUM, S., WARD, P. B., SILVA, E. S., HALLGREN, M., PONCE DE LEON, A., DUNN, A. L. & DESLANDES, A. C. 2018. Physical activity and incident depression: a meta-analysis of prospective cohort studies. *American Journal of Psychiatry*, 175, 631-648.
- SCOTT, I. C., WHITTLE, R., BAILEY, J., TWOHIG, H., HIDER, S. L., MALLIN, C. D., MULLER, S. & JORDAN, K. P. 2022. Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis epidemiology in England from 2004 to 2020: An observational study using primary care electronic health record data. *The Lancet Regional Health—Europe*, 23.
- SCOTT, S. N., COCKS, M., ANDREWS, R. C., NARENDRAN, P., PUREWAL, T. S., CUTHBERTSON, D. J., WAGENMAKERS, A. J. M. & SHEPHERD, S. O. 2018. High-Intensity Interval Training Improves Aerobic Capacity Without a Detrimental Decline in Blood Glucose in People With Type 1 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, 104, 604-612.
- SCOTT, S. N., SHEPHERD, S. O., ANDREWS, R. C., NARENDRAN, P., PUREWAL, T. S., KINNAFICK, F., CUTHBERTSON, D. J., ATKINSON-GOULDING, S., NOON, T. & WAGENMAKERS, A. J. 2019. A multidisciplinary evaluation of a virtually supervised home-based high-intensity interval training intervention in people with type 1 diabetes. *Diabetes care*, 42, 2330-2333.
- SEPPEL, B. F., DEN BOER, P., WIEGEL, J., TER WEE, M. M., VAN DER LEEDEN, M., DE VRIES, R., VAN DER ESCH, M. & BOS, W. H. 2020. Asynchronous mHealth interventions in rheumatoid arthritis: systematic scoping review. *JMIR mHealth and uHealth*, 8, e19260.
- SERRADOR, J. M., PICOT, P. A., RUTT, B. K., SHOEMAKER, J. K. & BONDAR, R. L. 2000. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke*, 31, 1672-1678.
- SHIMBO, D., ARTINIAN, N. T., BASILE, J. N., KRAKOFF, L. R., MARGOLIS, K. L., RAKOTZ, M. K. & WOZNIAK, G. 2020a. Self-Measured Blood Pressure Monitoring at Home: A Joint Policy Statement From the American Heart Association and American Medical Association. *Circulation*, 142, e42-e63.
- SHIMBO, D., ARTINIAN, N. T., BASILE, J. N., KRAKOFF, L. R., MARGOLIS, K. L., RAKOTZ, M. K., WOZNIAK, G., ASSOCIATION, A. H. & ASSOCIATION, T. A. M. 2020b. Self-measured blood pressure monitoring at home: a joint policy statement from the American Heart Association and American Medical Association. *Circulation*, 142, e42-e63.
- SHORE, C. B., HUBBARD, G., GORELY, T., POLSON, R., HUNTER, A. & GALLOWAY, S. D. 2019. Insufficient reporting of factors associated with exercise referral scheme

- uptake, attendance, and adherence: a systematic review of reviews. *Journal of Physical Activity and Health*, 16, 667-676.
- SHORT, C. E., FINLAY, A., SANDERS, I. & MAHER, C. 2018. Development and pilot evaluation of a clinic-based mHealth app referral service to support adult cancer survivors increase their participation in physical activity using publicly available mobile apps. *BMC Health Services Research*, 18, 27.
- SIM, J. & LEWIS, M. 2012. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *Journal of clinical epidemiology*, 65, 301-308.
- SIMPSON, D. & CLAASSEN, J. 2018. CrossTalk opposing view: dynamic cerebral autoregulation should be quantified using induced (rather than spontaneous) blood pressure fluctuations. *The Journal of physiology*, 596, 7.
- SINGH, K., DROUIN, K., NEWMARK, L. P., LEE, J., FAXVAAG, A., ROZENBLUM, R., PABO, E. A., LANDMAN, A., KLINGER, E. & BATES, D. W. 2016. Many mobile health apps target high-need, high-cost populations, but gaps remain. *Health Affairs*, 35, 2310-2318.
- SIQUEIRA, U. S., VALENTE, L. G. O., DE MELLO, M. T., SZEJNFELD, V. L. & PINHEIRO, M. M. 2017. Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-week intervention—the HyDRA trial. *American journal of physical medicine & rehabilitation*, 96, 167-175.
- SKEOCH, S. & BRUCE, I. N. 2015. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? *Nature Reviews Rheumatology*, 11, 390-400.
- SKOW, R. J., MACKAY, C. M., TYMKO, M. M., WILLIE, C. K., SMITH, K. J., AINSLIE, P. N. & DAY, T. A. 2013. Differential cerebrovascular CO₂ reactivity in anterior and posterior cerebral circulations. *Respiratory physiology & neurobiology*, 189, 76-86.
- SLADE, S. C., DIONNE, C. E., UNDERWOOD, M. & BUCHBINDER, R. 2016. Consensus on exercise reporting template (CERT): explanation and elaboration statement. *British journal of sports medicine*, 50, 1428-1437.
- SLADE, S. C., FINNEGAN, S., DIONNE, C. E., UNDERWOOD, M. & BUCHBINDER, R. 2018. The consensus on exercise reporting template (CERT) applied to exercise interventions in musculoskeletal trials demonstrated good rater agreement and incomplete reporting. *Journal of clinical epidemiology*, 103, 120-130.
- SLADE, S. C. & KEATING, J. L. 2012. Exercise prescription: a case for standardised reporting. *British journal of sports medicine*, 46, 1110-1113.
- SMIRL, J. D., HOFFMAN, K., TZENG, Y.-C., HANSEN, A. & AINSLIE, P. N. 2015. Methodological comparison of active-and passive-driven oscillations in blood pressure; implications for the assessment of cerebral pressure-flow relationships. *Journal of Applied Physiology*, 119, 487-501.
- SMITH, C. J., ALEXANDER, L. M. & KENNEY, W. L. 2013. Nonuniform, age-related decrements in regional sweating and skin blood flow. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 305, R877-R885.
- SOKKA, T., HÄKKINEN, A., KAUTIAINEN, H., MAILLEFERT, J. F., TOLOZA, S., MØRK HANSEN, T., CALVO - ALEN, J., ODING, R., LIVEBORN, M. & HUISMAN, M. 2008. Physical inactivity in patients with rheumatoid arthritis: data from twenty - one countries in a cross - sectional, international study. *Arthritis Care & Research: Official Journal of the American College of Rheumatology*, 59, 42-50.
- SOLOMON, D. H., CURTIS, J. R., SAAG, K. G., LII, J., CHEN, L., HARROLD, L. R., HERRINTON, L. J., GRAHAM, D. J., KOWAL, M. K. & KURIYA, B. 2013. Cardiovascular risk in rheumatoid arthritis: comparing TNF- α blockade with nonbiologic DMARDs. *The American journal of medicine*, 126, 730. e9-730. e17.

- SOLOMON, D. H., KARLSON, E. W., RIMM, E. B., CANNUSCIO, C. C., MANDL, L. A., MANSON, J. E., STAMPFER, M. J. & CURHAN, G. C. 2003. Cardiovascular Morbidity and Mortality in Women Diagnosed With Rheumatoid Arthritis. *Circulation*, 107, 1303-1307.
- SOWDEN, S. & RAINE, R. 2008. Running along parallel lines: how political reality impedes the evaluation of public health interventions. A case study of exercise referral schemes in England. *Journal of Epidemiology and Community Health*, 62, 835.
- SS MEEL-VAN DEN ABELEN, A., LAGRO, J., HEA VAN BEEK, A. & AHR CLAASSEN, J. 2014. Impaired cerebral autoregulation and vasomotor reactivity in sporadic Alzheimer's disease. *Current Alzheimer Research*, 11, 11-17.
- STATISTA. 2021. *Number of Wearable Device Users in the United States from 2014 to 2022 [Online]* [Online]. [Accessed].
- STAVROPOULOS-KALINOGLU, A., METSIOS, G. S., VAN ZANTEN, J. J. V., NIGHTINGALE, P., KITAS, G. D. & KOUTEDAKIS, Y. 2013. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. *Annals of the rheumatic diseases*, 72, 1819-1825.
- STEULTJENS, M., BELL, K. & HENDRY, G. 2023. The challenges of measuring physical activity and sedentary behaviour in people with rheumatoid arthritis. *Rheumatology Advances in Practice*, 7, rkac101.
- STEVENS, R. J., DOUGLAS, K. M., SARATZIS, A. N. & KITAS, G. D. 2005. Inflammation and atherosclerosis in rheumatoid arthritis. *Expert reviews in molecular medicine*, 7, 1-24.
- STUBBS, B., KOYANAGI, A., HALLGREN, M., FIRTH, J., RICHARDS, J., SCHUCH, F., ROSENBAUM, S., MUGISHA, J., VERONESE, N. & LAHTI, J. 2017. Physical activity and anxiety: A perspective from the World Health Survey. *Journal of affective disorders*, 208, 545-552.
- STUPIN, M., STUPIN, A., RASIC, L., COSIC, A., KOLAR, L., SERIC, V., LENASI, H., IZAKOVIC, K. & DRENJANCEVIC, I. 2018. Acute exhaustive rowing exercise reduces skin microvascular dilator function in young adult rowing athletes. *European journal of applied physiology*, 118, 461-474.
- SUMMERS, G., BOOTH, A., BROOKE-WAVELL, K., BARAMI, T. & CLEMES, S. 2019. Physical activity and sedentary behavior in women with rheumatoid arthritis: a comparison of patients with low and high disease activity and healthy controls. *Open access rheumatology : research and reviews*, 11, 133-142.
- SWEZEY, R. L. Essentials of physical management and rehabilitation in arthritis. *Seminars in Arthritis and Rheumatism*, 1974. Elsevier, 349-368.
- SYMMONS, D., TURNER, G., WEBB, R., ASTEN, P., BARRETT, E., LUNT, M., SCOTT, D. & SILMAN, A. 2002. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology*, 41, 793-800.
- TAN, C. O. 2012. Defining the characteristic relationship between arterial pressure and cerebral flow. *Journal of Applied Physiology*, 113, 1194-1200.
- TAYLOR, A., TAYLOR, R. S., INGRAM, W., DEAN, S. G., JOLLY, K., MUTRIE, N., LAMBERT, J., YARDLEY, L., STREETER, A. & GREAVES, C. 2021. Randomised controlled trial of an augmented exercise referral scheme using web-based behavioural support for inactive adults with chronic health conditions: the e-coacher trial. *British journal of sports medicine*, 55, 444-450.
- TAYLOR, A. H., DOUST, J. & WEBBORN, N. 1998. Randomised controlled trial to examine the effects of a GP exercise referral programme in Hailsham, East Sussex, on

- modifiable coronary heart disease risk factors. *Journal of Epidemiology & Community Health*, 52, 595-601.
- TEHAN, P. E., STEWART, S., CHUTER, V. H., CARROLL, M., RUTHERFURD, K. J. & BRENTON - RULE, A. 2019. Relationship between lower limb vascular characteristics, peripheral arterial disease and gait in rheumatoid arthritis. *International journal of rheumatic diseases*, 22, 2017-2024.
- TEMİZ, A., GÖKMEN, F., GAZI, E., AKBAL, A., BARUTÇU, A., BEKLER, A., ALTUN, B., TAN, Y., GÜNES, F. & SEN, H. 2015. Epicardial adipose tissue thickness, flow-mediated dilatation of the brachial artery, and carotid intima-media thickness. *Herz*, 40, 217.
- THIJSEN, D. H. J., BLACK, M. A., PYKE, K. E., PADILLA, J., ATKINSON, G., HARRIS, R. A., PARKER, B., WIDLANSKY, M. E., TSCHAKOVSKY, M. E. & GREEN, D. J. 2011. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. *American Journal of Physiology-Heart and Circulatory Physiology*, 300, H2-H12.
- THIJSEN, D. H. J., BRUNO, R. M., VAN MIL, A., HOLDER, S. M., FAITA, F., GREYLING, A., ZOCK, P. L., TADDEI, S., DEANFIELD, J. E., LUSCHER, T., GREEN, D. J. & GHIADONI, L. 2019. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J*.
- THOMAS, B. P., YEZHUVATH, U. S., TSENG, B. Y., LIU, P., LEVINE, B. D., ZHANG, R. & LU, H. 2013. Life - long aerobic exercise preserved baseline cerebral blood flow but reduced vascular reactivity to CO₂. *Journal of Magnetic Resonance Imaging*, 38, 1177-1183.
- THOMAS, J. G. & BOND, D. S. 2014. Review of innovations in digital health technology to promote weight control. *Current diabetes reports*, 14, 1-10.
- THOSAR, S. S., BIELKO, S. L., MATHER, K. J., JOHNSTON, J. D. & WALLACE, J. P. 2015. Effect of prolonged sitting and breaks in sitting time on endothelial function. *Med Sci Sports Exerc*, 47, 843-9.
- TIECKES, F. P., LAM, A. M., AASLID, R. & NEWELL, D. W. 1995. Comparison of Static and Dynamic Cerebral Autoregulation Measurements. *Stroke*, 26, 1014-1019.
- TREMBLAY, M. S., AUBERT, S., BARNES, J. D., SAUNDERS, T. J., CARSON, V., LATIMER-CHEUNG, A. E., CHASTIN, S. F. M., ALTENBURG, T. M., CHINAPAW, M. J. M., ALTENBURG, T. M., AMINIAN, S., ARUNDELL, L., ATKIN, A. J., AUBERT, S., BARNES, J., BARONE GIBBS, B., BASSETT-GUNTER, R., BELANGER, K., BIDDLE, S., BISWAS, A., CARSON, V., CHAPUT, J.-P., CHASTIN, S., CHAU, J., CHINAPAW, M., COLLEY, R., COPPINGER, T., CRAVEN, C., CRISTI-MONTERO, C., DE ASSIS TELES SANTOS, D., DEL POZO CRUZ, B., DEL POZO-CRUZ, J., DEMPSEY, P., DO CARMO SANTOS GONÇALVES, R. F., EKLUND, U., ELLINGSON, L., EZEUGWU, V., FITZSIMONS, C., FLOREZ-PREGONERO, A., FRIEL, C. P., FRÖBERG, A., GIANREGGORGIO, L., GODIN, L., GUNNELL, K., HALLOWAY, S., HINKLEY, T., HNATIUK, J., HUSU, P., KADIR, M., KARAGOUNIS, L. G., KOSTER, A., LAKERVELD, J., LAMB, M., LAROUCHE, R., LATIMER-CHEUNG, A., LEBLANC, A. G., LEE, E.-Y., LEE, P., LOPES, L., MANNS, T., MANYANGA, T., MARTIN GINIS, K., MCVEIGH, J., MENEGUCI, J., MOREIRA, C., MURTAGH, E., PATTERSON, F., RODRIGUES PEREIRA DA SILVA, D., PESOLA, A. J., PETERSON, N., PETTITT, C., PILUTTI, L., PINTO PEREIRA, S., POITRAS, V., PRINCE, S., RATHOD, A., RIVIÈRE, F., ROSENKRANZ, S., ROUTHIER, F., SANTOS, R., SAUNDERS, T., SMITH, B., THEOU, O., TOMASONE, J., TREMBLAY, M., TUCKER, P., UMSTATTD MEYER, R., VAN DER PLOEG, H., VILLALOBOS, T., VIREN, T., WALLMANN-SPERLICH, B., WIJNDAELE, K., WONDERGEM, R. & ON BEHALF OF, S. T. C. P. P. 2017. Sedentary Behavior Research Network (SBRN) – Terminology Consensus Project

- process and outcome. *International Journal of Behavioral Nutrition and Physical Activity*, 14, 75.
- TRICCO, A. C., LILLIE, E., ZARIN, W., O'BRIEN, K. K., COLQUHOUN, H., LEVAC, D., MOHER, D., PETERS, M. D., HORSLEY, T. & WEEKS, L. 2018. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Annals of internal medicine*, 169, 467-473.
- TZENG, Y.-C. & AINSLIE, P. N. 2014. Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *European journal of applied physiology*, 114, 545-559.
- UK CHIEF MEDICAL OFFICERS. 2019. *The UK Chief Medical Officers physical activity guidelines report. (cited 2019 Sept 9)*
<https://www.gov.uk/government/publications/physical-activity-guidelines-uk-chief-medical-officers-report> [Online]. [Accessed].
- UMPIERRE, D., RIBEIRO, P. A. B., KRAMER, C. K., LEITÃO, C. B., ZUCATTI, A. T. N., AZEVEDO, M. J., GROSS, J. L., RIBEIRO, J. P. & SCHAAN, B. D. 2011. Physical Activity Advice Only or Structured Exercise Training and Association With HbA1c Levels in Type 2 Diabetes: A Systematic Review and Meta-analysis. *JAMA*, 305, 1790-1799.
- UNGER, J. M., MOSELEY, A., SYMINGTON, B., CHAVEZ-MACGREGOR, M., RAMSEY, S. D. & HERSHMAN, D. L. 2018. Geographic distribution and survival outcomes for rural patients with cancer treated in clinical trials. *JAMA network open*, 1, e181235-e181235.
- VAN DEN BERG, M., RONDAY, H., PEETERS, A., LE CESSIE, S., VAN DER GIESEN, F., BREEDVELD, F. & VLIET VLIELAND, T. 2006. Using internet technology to deliver a home - based physical activity intervention for patients with rheumatoid arthritis: A randomized controlled trial. *Arthritis Care & Research: Official Journal of the American College of Rheumatology*, 55, 935-945.
- VAN DEN ENDE, C., HAZES, J., LE CESSIE, S., MULDER, W., BELFOR, D., BREEDVELD, F. & DIJKMANS, B. 1996. Comparison of high and low intensity training in well controlled rheumatoid arthritis. Results of a randomised clinical trial. *Annals of the rheumatic diseases*, 55, 798-805.
- VAN DEN ENDE, C. H., VLIET VLIELAND, T. P., MUNNEKE, M. & HAZES, J. M. 2000. Dynamic exercise therapy for rheumatoid arthritis. *Cochrane database of systematic reviews (Online)*, CD000322.
- VAN DOORNUM, S., MCCOLL, G., JENKINS, A., GREEN, D. & WICKS, I. 2003. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. *Arthritis & Rheumatism*, 48, 72-80.
- VAN DRONGELEN, V. & HOLOSHITZ, J. 2017. Human leukocyte antigen–disease associations in rheumatoid arthritis. *Rheumatic Disease Clinics*, 43, 363-376.
- VAN HALM, V., PETERS, M., VOSKUYL, A., BOERS, M., LEMS, W., VISSER, M., STEHOUWER, C., SPIJKERMAN, A., DEKKER, J. & NIJPELS, G. 2009. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Annals of the rheumatic diseases*, 68, 1395-1400.
- VAN HEES, V. T., FANG, Z., LANGFORD, J., ASSAH, F., MOHAMMAD, A., DA SILVA, I. C., TRENELL, M. I., WHITE, T., WAREHAM, N. J. & BRAGE, S. 2014a. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. *J Appl Physiol (1985)*, 117, 738-44.
- VAN HEES, V. T., FANG, Z., LANGFORD, J., ASSAH, F., MOHAMMAD, A., DA SILVA, I. C., TRENELL, M. I., WHITE, T., WAREHAM, N. J. & BRAGE, S. 2014b. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity

- and temperature: an evaluation on four continents. *Journal of applied physiology*, 117, 738-744.
- VAN HEES, V. T., GORZELNIAK, L., DEAN LEÓN, E. C., EDER, M., PIAS, M., TAHERIAN, S., EKELUND, U., RENSTRÖM, F., FRANKS, P. W. & HORSCH, A. 2013a. Separating movement and gravity components in an acceleration signal and implications for the assessment of human daily physical activity. *PloS one*, 8, e61691.
- VAN HEES, V. T., GORZELNIAK, L., DEAN LEÓN, E. C., EDER, M., PIAS, M., TAHERIAN, S., EKELUND, U., RENSTRÖM, F., FRANKS, P. W., HORSCH, A. & BRAGE, S. 2013b. Separating movement and gravity components in an acceleration signal and implications for the assessment of human daily physical activity. *PLoS One*, 8, e61691.
- VELDHUIJZEN VAN ZANTEN, J. J., ROUSE, P. C., HALE, E. D., NTOUMANIS, N., METSIOS, G. S., DUDA, J. L. & KITAS, G. D. 2015a. Perceived barriers, facilitators and benefits for regular physical activity and exercise in patients with rheumatoid arthritis: a review of the literature. *Sports medicine*, 45, 1401-1412.
- VELDHUIJZEN VAN ZANTEN, J. J. C. S., ROUSE, P. C., HALE, E. D., NTOUMANIS, N., METSIOS, G. S., DUDA, J. L. & KITAS, G. D. 2015b. Perceived Barriers, Facilitators and Benefits for Regular Physical Activity and Exercise in Patients with Rheumatoid Arthritis: A Review of the Literature. *Sports Medicine*, 45, 1401-1412.
- VEMULAPALLI, S., DOLOR, R. J., HASSELBLAD, V., SCHMIT, K., BANKS, A., HEIDENFELDER, B., PATEL, M. R. & JONES, W. S. 2015. Supervised vs unsupervised exercise for intermittent claudication: a systematic review and meta-analysis. *American Heart Journal*, 169, 924-937. e3.
- VERHOEVEN, F., PRATI, C., CHOUK, M., DEMOUGEOT, C. & WENDLING, D. 2021. Methotrexate and cardiovascular risk in rheumatic diseases: A comprehensive review. *Expert Review of Clinical Pharmacology*, 14, 1105-1112.
- VERNIERI, F., TIBUZZI, F., PASQUALETTI, P., ROSATO, N., PASSARELLI, F., ROSSINI, P. M. & SILVESTRINI, M. 2004. Transcranial Doppler and Near-Infrared Spectroscopy Can Evaluate the Hemodynamic Effect of Carotid Artery Occlusion. *Stroke*, 35, 64-70.
- VESSEY, M., VILLARD-MACKINTOSH, L. & YEATES, D. 1987. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. *Contraception*, 35, 457-464.
- VICKERS, A. J. & ALTMAN, D. G. 2001. Analysing controlled trials with baseline and follow up measurements. *Bmj*, 323, 1123-1124.
- VINK, A., SCHONEVELD, A. H., POPPEN, M., DE KLEIJN, D. P., BORST, C. & PASTERKAMP, G. 2002. Morphometric and immunohistochemical characterization of the intimal layer throughout the arterial system of elderly humans. *Journal of anatomy*, 200, 97-103.
- WÅLLBERG - JONSSON, S., CAIDAH, K., KLINTLAND, N., NYBERG, G. & RANTAPÄÄ - DAHLQVIST, S. 2008. Increased arterial stiffness and indication of endothelial dysfunction in long - standing rheumatoid arthritis. *Scandinavian journal of rheumatology*, 37, 1-5.
- WARBURTON, D. E. R., NICOL, C. W. & BREDIN, S. S. D. 2006. Health benefits of physical activity: the evidence. *Canadian Medical Association Journal*, 174, 801.
- WARE JR, J. E. 2000. SF-36 health survey update. *Spine*, 25, 3130-3139.
- WEBSTER, K., CELLA, D. & YOST, K. 2003. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes*, 1, 79.
- WELLS, G. A. 2009. Patient-Driven Outcomes in Rheumatoid Arthritis. *The Journal of Rheumatology*, 82, 33.
- WHO, W. H. O. 2020. Physical activity Fact sheet.

- WILCOX, S., DER ANANIAN, C., ABBOTT, J., VRAZEL, J., RAMSEY, C., SHARPE, P. A. & BRADY, T. 2006. Perceived exercise barriers, enablers, and benefits among exercising and nonexercising adults with arthritis: results from a qualitative study. *Arthritis Care & Research: Official Journal of the American College of Rheumatology*, 55, 616-627.
- WILKE, J., MOHR, L., TENFORDE, A. S., EDOUARD, P., FOSSATI, C., GONZÁLEZ-GROSS, M., SÁNCHEZ RAMÍREZ, C., LAÍÑO, F., TAN, B. & PILLAY, J. D. 2021. A pandemic within the pandemic? Physical activity levels substantially decreased in countries affected by COVID-19. *International Journal of Environmental Research and Public Health*, 18, 2235.
- WILLIE, C., COLINO, F., BAILEY, D., TZENG, Y., BINSTED, G., JONES, L., HAYKOWSKY, M., BELLAPART, J., OGOH, S. & SMITH, K. 2011. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. *Journal of neuroscience methods*, 196, 221-237.
- WILLIE, C., MACLEOD, D., SHAW, A., SMITH, K., TZENG, Y.-C., EVES, N., IKEDA, K., GRAHAM, J., LEWIS, N. & DAY, T. 2012. Regional brain blood flow in man during acute changes in arterial blood gases. *The Journal of physiology*, 590, 3261-3275.
- WILLIE, C. K., TZENG, Y. C., FISHER, J. A. & AINSLIE, P. N. 2014. Integrative regulation of human brain blood flow. *The Journal of physiology*, 592, 841-859.
- WISEMAN, S. J., RALSTON, S. H. & WARDLAW, J. M. 2016. Cerebrovascular disease in rheumatic diseases: a systematic review and meta-analysis. *Stroke*, 47, 943-950.
- WOODMAN, R. J., PLAYFORD, D. A., WATTS, G. F., CHEETHAM, C., REED, C., TAYLOR, R. R., PUDDEY, I. B., BEILIN, L. J., BURKE, V., MORI, T. A. & GREEN, D. 2001. Improved analysis of brachial artery ultrasound using a novel edge-detection software system. *Journal of Applied Physiology*, 91, 929-937.
- WORLD HEALTH ORGANISATION 2011. mHealth: new horizons for health through mobile technologies. *mHealth: new horizons for health through mobile technologies*.
- WORLD HEALTH ORGANISATION 2017. Frequently asked questions on Global Task Force on digital health for TB and its work. *World Health Organization Tuberculosis (TB)*. *World Health Organization*.
- WORLD HEALTH ORGANISATION 2020. WHO guidelines on physical activity and sedentary behaviour.
- [WWW.LECTURIO.COM](https://www.lecturio.com). 2024. Available: <https://www.lecturio.com/concepts/cerebrovascular-system/> [Accessed 28.02.24].
- XU, S.-Z., WANG, P., GUAN, S.-Y., LI, H.-M., LENG, R.-X., PAN, H.-F. & YE, D.-Q. 2017. Decreased flow-mediated dilatation in patients with rheumatoid arthritis: a meta-analysis. *Postgraduate Medical Journal*, 93, 260-265.
- YAN, J., YANG, S., HAN, L., BA, X., SHEN, P., LIN, W., LI, T., ZHANG, R., HUANG, Y. & HUANG, Y. 2023. Dyslipidemia in rheumatoid arthritis: the possible mechanisms. *Frontiers in Immunology*, 14.
- YATES, T., GRAY, L. J., HENSON, J., EDWARDSON, C. L., KHUNTI, K. & DAVIES, M. J. 2019. Impact of depression and anxiety on change to physical activity following a pragmatic diabetes prevention program within primary care: pooled analysis from two randomized controlled trials. *Diabetes Care*, 42, 1847-1853.
- YKI-JÄRVINEN, H., BERGHOLM, R. & LEIRISALO-REPO, M. 2003. Increased inflammatory activity parallels increased basal nitric oxide production and blunted response to nitric oxide in vivo in rheumatoid arthritis. *Annals of the rheumatic diseases*, 62, 630-634.

- YOUNG, L., BARNASON, S. & DO, V. 2015. Review strategies to recruit and retain rural patient participating self-management behavioral trials. *Online journal of rural research and policy*, 10, 1.
- YUAN, S. Y., RIGOR, R. R. & RIGOR, R. 2011. Regulation of endothelial barrier function.
- ZHANG, R., ZUCKERMAN, J. H., GILLER, C. A. & LEVINE, B. D. 1998. Transfer function analysis of dynamic cerebral autoregulation in humans. *American Journal of Physiology-Heart and Circulatory Physiology*, 274, H233-H241.
- ZHANG, S., LIU, Y., CAO, Y., ZHANG, S., SUN, J., WANG, Y., SONG, S. & ZHANG, H. 2022. Targeting the microenvironment of vulnerable atherosclerotic plaques: an emerging diagnosis and therapy strategy for atherosclerosis. *Advanced Materials*, 34, 2110660.

CHAPTER 9: APPENDICES

9.1. Chapter 3 Supplementary Material

9.1.1. List of supplementary material

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9.1.2. Supplementary files

9.1.2.1. Supplementary File 1. CONSORT extension for Pilot and Feasibility Trials Checklist



CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	3-4
	2b	Specific objectives or research questions for pilot trial	4
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5, 13-14
	4c	How participants were identified and consented	5-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-9
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	9-16
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A

	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	9-16
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	17, Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	17
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Table 4
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Table 4

Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Figure 1-4, Table 1-4, Supp Figure 1-2 and Tables 3-4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	33
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	27-33
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	27-33
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	27-33
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	5
Protocol	24	Where the pilot trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	34
	26	Ethical approval or approval by research review committee, confirmed with reference number	5

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

9.1.2.2. Supplementary File 2. Template for Intervention Description and Replication (TIDieR)



The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other [†] (details)
1.	BRIEF NAME Provide the name or a phrase that describes the intervention.	1	Line 8
2.	WHY Describe any rationale, theory, or goal of the elements essential to the intervention.	10	Lines 4-11
3.	WHAT Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	6-10	Pg6 Line 18 - Pg10 Line 2
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	6-10	Pg6 Line 18 - Pg10 Line 2
5.	WHO PROVIDED For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given. HOW	7	Lines 18-20

6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group. WHERE	7	Pg 7 Lines 1-3, 12-16
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	7	Pg 7 Lines 1-3, 12-16
WHEN and HOW MUCH			
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose. TAILORING	6	Lines 18-20
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how. MODIFICATIONS	7-8	Pg7 Line 17-Pg 8 Line 8
10.*	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how). HOW WELL	9	Lines14-23
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	10-12	Pg10 Line 15- Pg12 Line 21
12.*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	19	Lines 1-7 Table 2

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use ‘?’ if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

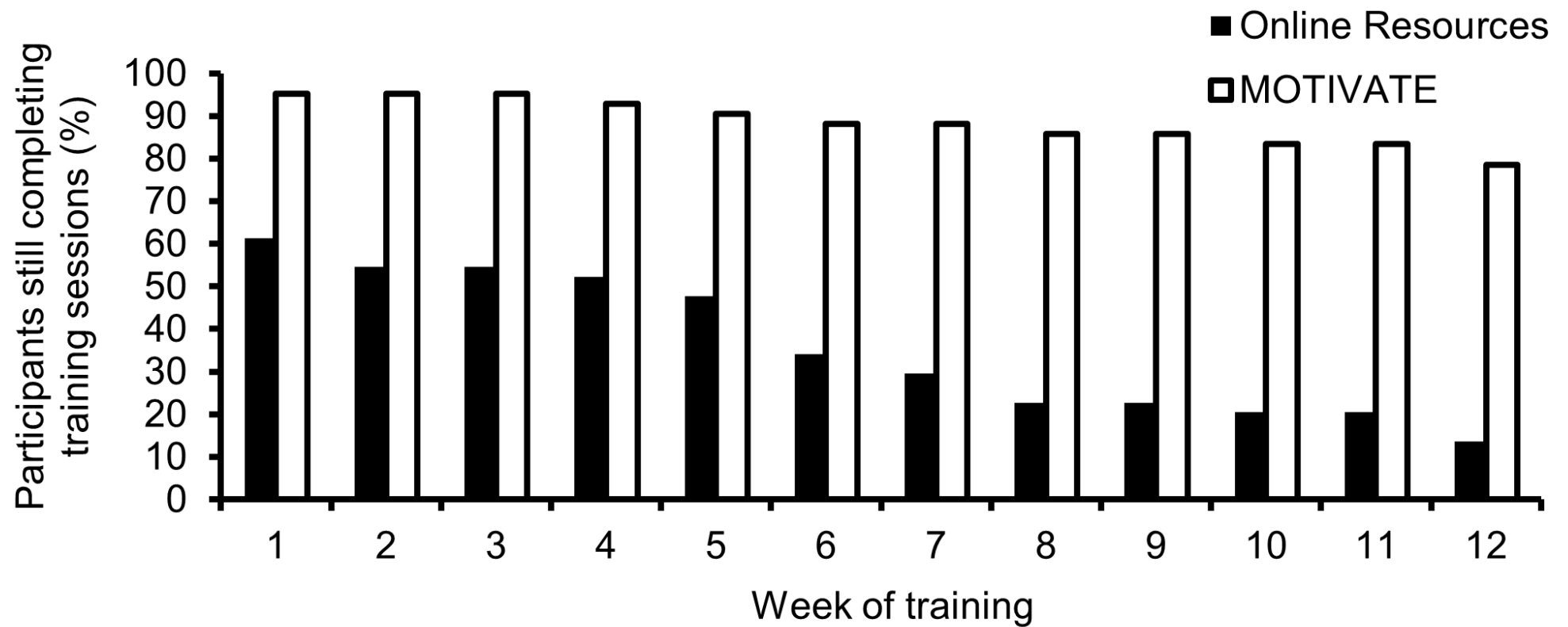
‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

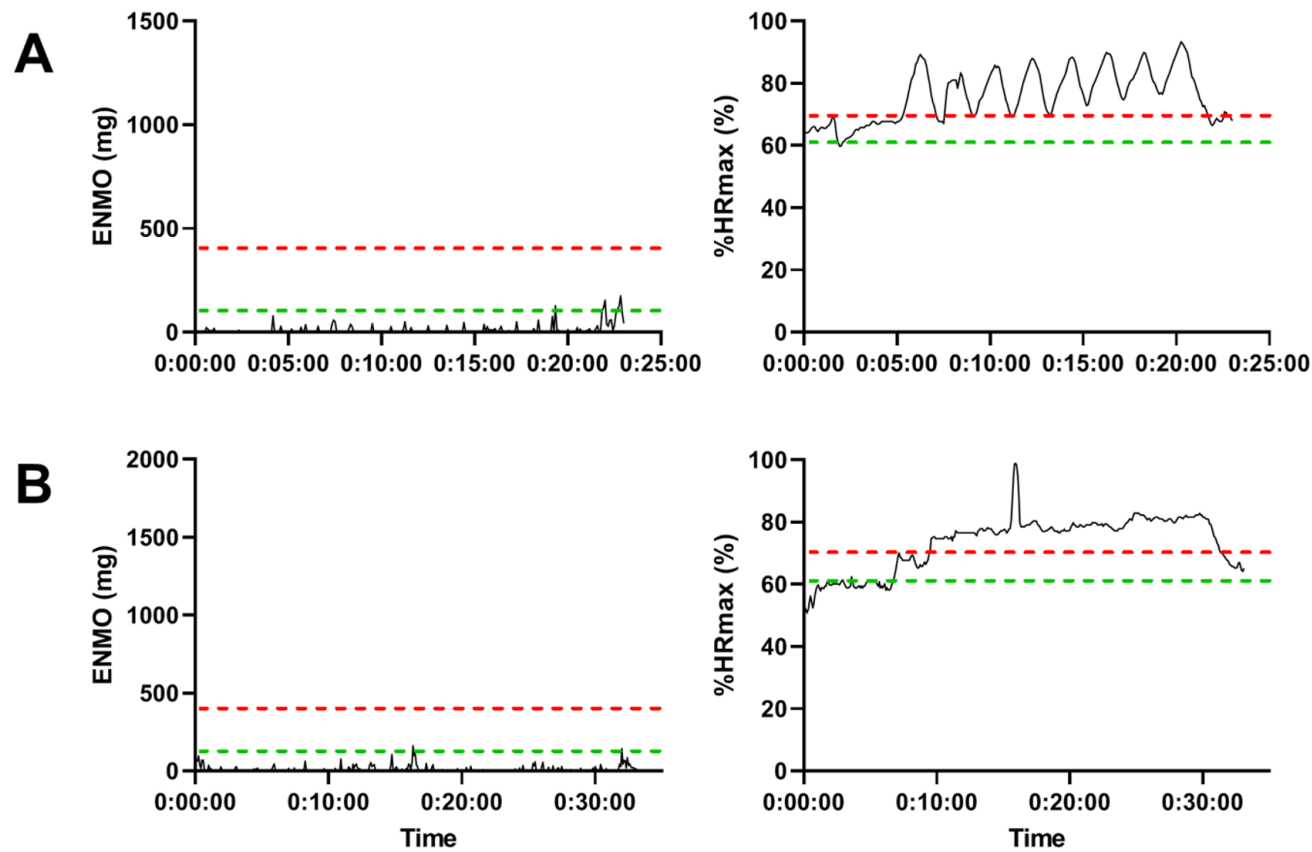
* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement**. When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

9.1.3. Supplementary figures

9.1.3.1. Supplementary Figure 1. A percentage of participants still completing training sessions.



9.1.3.2. Supplementary Figure 2. Accelerometer (mg) and HR data (%HRmax) traces recorded throughout bouts of HIIT (A) and VIT (B) conducted on a cycle ergometer. Red line is indicative of the vigorous intensity threshold (>429mg/70%HRmax), green line is indicative of the moderate intensity threshold (>101mg/60%HRmax).



9.1.4. Supplementary tables

9.1.4.1. *Supplementary Table 1. Exercise prescription for moderate-intensity continuous training*

Week	Total Session Duration (min)	Warm-up: Workout Duration (min)	Intensity (%HR _{max}) (Warm-up: Workout)
1-2	25	5:20	
3-4	30	5:25	
5-6	35	5:30	50-60:
7-8	40	5:35	50-70
9-10	45	5:40	
11-12	50	5:45	

9.1.4.2. Supplementary Table 2. Exercise prescription for vigorous-intensity training

Week	Total Session Duration (min)	Low:High Workout Duration (min)	Warm-up: High: Low Phase Duration (min)	Repetition of Phases	Intensity (%HR _{Max}) (Low:High)
1	20	14:6	5:2:3	3	50-60: 60-70
2	20	14:6	5:3:2	3	50-60: 60-70
3	25	13:12	5:3:2	4	50-60: 65-75
4	25	13:12	5:4:1	4	50-60: 65-75
5	25	9:16	5:4:1	4	50-60: 70-80
6	25	9:16	5:4:1	4	50-60: 70-80
7	29	9:20	5:5:1	4	50-60: 70-80
8	32	8:24	5:8:1	3	50-60: 70-80
9	30	7:24	5:12:1	2	50-60: 70-80
10	30	7:24	5:12:1	2	50-60: 70-80
11	30	5:25	5:25:0	1	50-60: 70-80
12	30	5:25	5:25:0	1	50-60: 70-80

9.1.4.3. Supplementary Table 3. Exercise prescription for high-intensity interval training

Week	Total Session Duration (min)	Warm-up: Workout Duration	No Intervals	Intensity (%HR _{Max}) (Warm-up: Workout)	
1-2	12	2:10	5	50-70:	≥80
3-4	14	2:12	6		
5-6	16	2:14	7		
7-8	18	2:16	8		
9-10	20	2:18	9		
11-12	22	2:20	10		

9.1.4.4. Supplementary Table 4. Exercise prescription for resistance training

Week	Total Session Duration (min)	Warm-up: Workout Duration	No. of exercises	No of Sets	Time per set (s)	Rest between exercises/sets (s)
1-2	26	2: 24	5	3	30	60/120
3-4	28	2: 26			40	60/120
5-6	28	2:26			50	45/120
7-8	39	2:37	6	4	40	45/120
9-10	38	2:36			50	30/120
11-12	42	2:40			60	30/120

9.1.4.5. Supplementary Table 5. Details of the counselling intervention

	Date		Details
Consultation 1	Prior to intervention		Initial meeting to assess current beliefs/concerns, explore the benefits of exercise and agree on a SMART (specific, measurable, achievable, relevant and time-bound) plan
Consultation 2	Prior to intervention		Development of the personal exercise program and education on how to use the mHealth technology
Consultation 3	4 weeks		Patient feedback and refinement of the exercise program with the aim of progressing the program. Data recorded in the smart phone app and online coaching platform was used to guide discussions
Consultation 4	12 weeks		Patient feedback and review of progress. Discussion on strategies for maintaining exercise and PA. Data recorded in the smart phone app and online coaching platform was used to guide discussions

9.1.4.6. Supplementary Table 6. Topic guide baseline interviews.

Key questions	Probes
How did you find the resources and training provided before the home testing?	○ How did it help (videos, booklets, checklist, phone call with researcher) ○ Would you have found it useful for the researcher to be with you during the testing, via video or phone? ○ Recommendations for improvement
Did you have any issues receiving the testing package?	
What did you think about the measures you collected during the scheme?	○ Thoughts on specific outcome measures (questionnaires/bloods/blood pressure etc) ○ Understanding; interest; comfort; difficulty ○ Number of measures ○ Do you think we measured important outcomes?
What did you think about the 7-day period where you wore the PA monitor and flash glucose monitor (explain FGM if needed)?	○ Activity monitor ○ Understanding; interest; comfort; difficulty ○ Number of measures ○ Do you think we measured what was important? Did we miss anything? ○ Was it easy to return the monitors to the research team? MOTIVATE only: ○ Was it easy to download and use the mobile Apps (Zoom and Polar Flow)? MOTIVATE only: ○ Was it easy to pair the devices (Polar Flow, Ignite, OH1)?

9.1.4.7. Supplementary Table 7. Topic guide post-intervention interviews for MOTIVATE participants.

Key questions	Probes
Can you talk me through your experience of the exercise programme?	○ types of exercise; difficulty; progression; engaging; choice ○ Anything you didn't like / found difficult ○ Recommendations for improvement
How well supported did you feel in terms of the exercise advice?	○ Did you feel more or less supported by joining the study? ○ Who supported you? ○ Do you think this helped your exercise behaviour?
Is there any additional support that could have further encourage you to exercise?	
Do you feel more or less confident about taking part in exercise following the intervention?	
Did you find any factors particularly helpful in increasing your exercise levels?	
Did you face any barriers to increasing your exercise levels?	○ Did you overcome these: if so, how?
How useful do you feel the exercise counselling sessions were for supporting a change in your exercise habits?	○ What were the pro and cons of talking to your exercise specialist? ○ Would sessions have been better face-to-face? ○ Session duration ○ Number/ frequency of sessions
Did the text messages from your exercise specialist encourage you to keep exercising?	○ Could the language in text have been improved? ○ Number/ frequency of texts ○ Did you feel able to reply to the messages?
How useful did you find the mobile App (Polar Flow) for supporting a change in your exercise habits?	○ How useful did you find the activity target? ○ Did you encounter any problems with the App? ○ How user friendly was the App? ○ How often did you look at the app? ○ Was the watch easy to use (difficulties syncing the watch and App)?

How useful did you find the fitness watch (Polar Flow) for supporting a change in your exercise habits?	☐ Did you like the design of the watch (bulky, big enough screen)? ☐ Did the pre-set exercise sessions help you? ☐ Would you change the watch face in any way? ☐ Did you find HR feedback useful?
Do you think the MOTIVATE LJMU website supported a change in your exercise habits?	☐ Elements of the website that worked well ☐ Elements of the website that could be improved
Which additional support element (App, texts, watch, website) did you find most useful for supporting a change in your exercise habits?	
Where did you first hear about the trial from? Who approached you?	
What appealed to you about taking part in the study in the first place? What were your reasons?	
Was there anything that put you off taking part in the study?	
Did the study meet your expectations from the advertisements, PIS and initial meeting?	
How easy was it to complete the measures at home?	
Did you feel well supported taking measures at home?	
How easy to complete and understand were the questionnaires you received?	
Was communication with the research team well managed?	

If there was one thing we could do to make the study easier for you to take part in, what would it be?

We are planning to undertake a larger scale study similar to the one you have taken part in. What sort of things would you change about the study that might make people want to take part in it more?

Overall, what did you feel was good or bad about taking part in the study?

9.1.4.8. Supplementary Table 8. Topic guide post-intervention interviews for online resources participants.

Key questions	Probes
Can you talk me through your experience of the exercise programme?	○ types of exercise; difficulty; progression; engaging; choice ○ Anything you didn't like / found difficult
How well supported did you feel in terms of the exercise advice?	○ Recommendations for improvement
Is there any additional support that could have further encourage you to exercise?	○ Did you feel more or less supported by joining the study? ○ Who supported you? ○ Do you think this helped your exercise behaviour?
Do you feel more or less confident about taking part in exercise following the intervention?	
Did you find any factors particularly helpful in increasing your exercise levels?	
Did you face any barriers to increasing your exercise levels?	○ Did you overcome these: if so how?
Do you think the MOTIVATE LJMU website supported a change in your exercise habits?	○ Elements of the website that worked well ○ Elements of the website that could be improved
Did you like the OH1?	○ What didn't you like about it? ○ Did you forget to wear the OH1? ○ Did you ever forget to start and stop the session? ○ Would you use the OH1 in the same way (to gather more data) after the study?
Where did you first hear about the trial from? Who approached you?	
What appealed to you about taking part in the study in the first place? What were your reasons?	

Was there anything that put you off taking part in the study?

Did the study meet your expectations from the advertisements, PIS and initial meeting?

How easy was it to complete the measures at home?

Did you feel well supported taking measures at home?

How easy to complete and understand were the questionnaires you received?

Was communication with the research team well managed?

If there was one thing we could do to make the study easier for you to take part in what would it be?

We are planning to undertake a larger scale study similar to the one you have taken part in. What sort of things would you change about the study that might make people want to take part in it more?

Overall, what did you feel was good or bad about taking part in the study?

9.1.4.9. Supplementary Table 9. Compliance criteria for exercise types

Exercise type	Duration	Compliance criteria	
		Intensity	
MICT	≥ what was prescribed	Mean session HR ≥ 60% HR _{max}	
VIT	≥ what was prescribed	Mean session HR ≥ the predicted mean HR (based on the prescription, see Supplementary Table 6)	
HIIT	Completed the prescribed number of intervals	Achieving a HR ≥80% HR _{max} during the session	
RT	≥ what was prescribed	N/A	

MICT; moderate-intensity continuous training, VIT; vigorous-intensity training, HIIT; high-intensity interval training, RT; resistance training, HR; heart rate, HR_{max}; heart rate maximum predicted using 220-age.

9.1.4.10. Supplementary Table 10. Survey questions post-intervention for MOTIVATE participants.

Question	
1	Did you find any factors particularly helpful in increasing your exercise levels. Please provide up to three facilitators
2	What barriers did you face to increasing your exercise levels. Please provide up to three barriers
3	What did you like about the extra support (e.g. Polar Flow app, fitness watch, counselling sessions and feedback from researcher and HR feedback during exercise)? What could be improved?
4	What did you like about the counselling sessions? What could be improved
5	What did you like about the text messages? What could be improved
6	Were there any challenges to accessing or using the participant app? How could these challenges be overcome?
7	Were there any challenges to using the fitness watch? How could these challenges be overcome?
8	Were there any challenges to using the website? How do you think these challenges could be overcome?

9.1.4.11. *Supplementary Table 11. Survey questions post-intervention for online resources participants.*

Questions	
1	Did you find any factors particularly helpful in increasing your exercise levels. Please provide up to three facilitators
2	What barriers did you face to increasing your exercise levels. Please provide up to three barriers
3	Were there any challenges to using the website? How do you think these challenges could be overcome?

9.1.4.12. *Supplementary Table 12. Survey question following baseline measures.*

1.	Did you have any issues receiving the testing equipment parcel?					
	Yes	No				
2.	For each of the procedures how easy did you find taking the measure at home?					
		Extremely easy	Very easy	Somewhat easy	Slightly easy	Not at all easy
	Measuring your height					
	Measuring your weight					
	Measuring your waist circumference					
	Taking your blood pressure					
3.	How easy did you find completing the questionnaires online					
		Extremely easy	Very easy	Somewhat easy	Slightly easy	Not at all easy
4.	Was it easy to post these devices back to the research team					
		Extremely easy	Very easy	Somewhat easy	Slightly easy	Not at all easy

9.1.4.13. Supplementary Table 13. Perceived facilitators and barriers to exercise between intervention groups.

Numbers indicate the number of participants that gave a response related to each theme. Representative participant quotes are placed below each theme and sub-theme.

Theme	Subtheme	MOTIVATE		Online Resources	
		Positive Responses	Negative Responses	Positive Responses	Negative Responses
Motivation	Accountability	Being Monitored by the team (13), being part of the study (2), health Check (1)		Being part of the study (4), health Check (2)	
		<i>"Having someone monitoring it without being present"</i>		<i>"A sense of commitment by being part of the programme."</i>	
	Communication and feedback	Text messages (17), regular guidance (28), counselling sessions (1)			
		<i>"Text messages checking in on me and commenting on my sessions helped motivate me"</i>			
	Tracking	Using app to track (16), real-Time Heart rate Feedback (19)		Wearing a monitor (7)	

	<i>"The polar flow app and fitness watch was really useful in monitoring my activity and pushing me to ensure I hit my daily goal."</i>		<i>"Wearing the Polar [OH1] heart rate monitor when exercising"</i>	
Flexibility of the Intervention	Programme to follow (13), flexible programme (4), progressive programme (5), personalised (7), resources (2)	Work/life balance (15), lack of time (7), lack of motivation (2), tiredness (1)	Programme to follow (8), resources (8)	Work/life balance (10), lack of time (9), lack of Motivation (2), tiredness (8)
	<i>"I liked the fact that it was tailored toward myself and what I wanted to achieve and complete"</i>	<i>"Long workdays made me tired, and I didn't want to go out."</i>	<i>"Having access to online videos to guide me through exercise"</i>	<i>"Sometimes difficult to find time in a busy workday to exercise."</i>
Environmental	Social support (2)	Health (12), weather (5), social Support (1)	Weather (3), social support (1)	Health (13), weather (8),
	<i>"Other people I knew were on the programme"</i>	<i>"Bad weather makes me not want to go outside"</i>	<i>"Planning time for it when good weather "</i>	<i>"Suffered with various injuries and not resting long enough to recover"</i>
Covid	Health Concerns as a result of COVID (1), change in schedule (1)	Unable to access facilities (4), isolating (3), ill health due to COVID (1)	Health Concerns as a result of COVID (3), change in schedule (2)	Unable to access facilities (1), isolating (3), ill health due to COVID (2)

<i>“Working from home”</i>	<i>“Having to self-isolate”</i>	<i>“The potential impact of Covid on overweight people like myself “</i>	<i>“Being classed as vulnerable and advised not to go to the gym owing to Covid”</i>
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9.1.4.14. Supplementary Table 14. Responses from the baseline testing survey

	Yes	No			
	n (%)	n (%)			
Did you have any issues receiving the testing equipment parcel?	8 (9.6)	75 (90.4)			
	Extremely easy n (%)	Very easy n (%)	Somewhat easy n (%)	Slightly easy n (%)	Not at all easy n (%)
For each of the procedures how easy did you find taking the measure at home?					
Height	40 (48.2)	35 (42.2)	6 (7.2)	0 (0)	2 (2.4)
Weight	68 (84)	13 (16)	0 (0)	0 (0)	0 (0)
Waist circumference	47 (56.6)	27 (32.5)	7 (8.4)	1 (1.2)	1 (1.2)
Blood pressure	39 (47.6)	29 (35.4)	12 (14.6)	2 (2.4)	0 (0)
How easy did you find completing the questionnaires online?	59 (71.1)	23 (27.7)	1 (1.2)	0 (0)	0 (0)
Was it easy to post these devices back to the research team?	58 (75.3)	14 (18.2)	3 (3.9)	2 (2.6)	(0)

9.2. Chapter 6 Supplementary Material

9.2.1. Supplementary File 1. Search parameters

((("rheumatoid arthritis"[Title/Abstract] OR "caplan syndrome"[Title/Abstract] OR "felty syndrome"[Title/Abstract] OR "rheumatoid nodule"[Title/Abstract] OR "rheumatoid vasculitis"[Title/Abstract] OR "sjogren's syndrome"[Title/Abstract] OR "still's disease"[Title/Abstract])) AND ("exercise"[Title/Abstract] OR "sport*" [Title/Abstract] OR "physical activity"[Title/Abstract] OR "physiotherapy"[Title/Abstract] OR "fitness"[Title/Abstract] OR "accelerometer"[Title/Abstract] OR "aerobic"[Title/Abstract] OR "resistance training"[Title/Abstract] OR "strength training"[Title/Abstract] OR "swimming"[Title/Abstract] OR "lifestyle"[Title/Abstract] OR "physical conditioning"[Title/Abstract] OR "gymnastics"[Title/Abstract] OR "running"[Title/Abstract] OR "jogging"[Title/Abstract] OR "sitting"[Title/Abstract] OR "sedentary behavior"[Title/Abstract] OR "sedentary behaviour"[Title/Abstract] OR "sedentarism"[Title/Abstract] OR "walking"[Title/Abstract] OR "cycling"[Title/Abstract] OR "calisthenic*" [Title/Abstract] OR "Tai chi"[Title/Abstract] OR "yoga"[Title/Abstract])) AND ("Clinical trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Study"[Publication Type] OR "Trial" [Title/Abstract])

9.2.2. Supplementary File 2. Consensus on Exercise Reporting Template (CERT)

CERT ✓ Consensus on Exercise Reporting Template

A Checklist for what to include when reporting exercise programs

Section/Topic	Item #	Checklist item	Location **	
			Primary paper (page, table, appendix)	† Other (paper or protocol, website (URL)
WHAT: materials	1	Detailed description of the type of exercise equipment (e.g. weights, exercise equipment such as machines, treadmill, bicycle ergometer etc)	_____	_____
WHO: provider	2	Detailed description of the qualifications, teaching/supervising expertise, and/or training undertaken by the exercise instructor	_____	_____
HOW: delivery	3	Describe whether exercises are performed individually or in a group	_____	_____
	4	Describe whether exercises are supervised or unsupervised and how they are delivered	_____	_____
	5	Detailed description of how adherence to exercise is measured and reported	_____	_____
	6	Detailed description of motivation strategies	_____	_____
	7a	Detailed description of the decision rule(s) for determining exercise progression	_____	_____
	7b	Detailed description of how the exercise program was progressed	_____	_____
	8	Detailed description of each exercise to enable replication (e.g. photographs, illustrations, video etc)	_____	_____
	9	Detailed description of any home program component (e.g. other exercises, stretching etc)	_____	_____
	10	Describe whether there are any non-exercise components (e.g. education, cognitive behavioural therapy, massage etc)	_____	_____
	11	Describe the type and number of adverse events that occurred during exercise	_____	_____

WHERE: location	12	Describe the setting in which the exercises are performed		
WHEN, HOW MUCH: dosage	13	Detailed description of the exercise intervention including, but not limited to, number of exercise repetitions/sets/sessions, session duration, intervention/program duration etc		
TAILORING: what, how	14a	Describe whether the exercises are generic (one size fits all) or tailored whether tailored to the individual		
	14b	Detailed description of how exercises are tailored to the individual		
	15	Describe the decision rule for determining the starting level at which people commence an exercise program (such as beginner, intermediate, advanced etc)		
HOW WELL: planned, actual	16a	Describe how adherence or fidelity to the exercise intervention is assessed/measured		
	16b	Describe the extent to which the intervention was delivered as planned		

***It is recommended that this checklist is used in conjunction with the Explanation and Elaboration Statement which is a guide each item in the CERT Checklist**

The CERT Checklist is designed for reporting details of an exercise intervention. The CERT Checklist should be used in conjunction with a reporting checklist appropriate for the study type e.g. the CONSORT Statement (www.consort-statement.org) for randomised controlled trials, the SPIRIT Statement (www.spirit-statement.org) for a clinical trial protocol. For further guidance regarding reporting guidelines please consult the EQUATOR network (www.equator-network.org)

** Authors – please use N/A if an item is not applicable Reviewers – please use “?” if information is not provided or not/insufficiently reported

† If the information is not provided in the primary paper that is under consideration, please provide details of where this information is available e.g. in a published protocol, published papers (provide citation details) or on a website (provide the URL).