What is the impact of early adult rheumatoid arthritis on the biomechanical and functional characteristics of the foot and lower limb?

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A thesis in partial fulfilment of the requirements of the University of East London for a degree of Doctor of Philosophy

February 2019

Declaration

I declare that while registered as a research degree student at UEL, I have not been a registered or enrolled student for another award of this university or of any other academic or professional institution. I declare that no material contained in the thesis has been used in any other submission for an academic award.

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Abstract

Early rheumatoid arthritis may be characterized by the rapid onset of functional impairment. Despite advancements in the management of this disease, more than half of all patients experience significant walking impairments within the first two years following diagnosis. Clinical research has adopted 3D motion capture to provide data on musculoskeletal impairment in rheumatoid arthritis. However, there is limited published research using 3D motion capture to investigate the effects of early rheumatoid arthritis on the biomechanical function of the foot and lower limb. To translate laboratory based findings into clinical practice, more comprehensive data are therefore required in order to optimise the recognition and targeted management of early musculoskeletal pathology in rheumatoid arthritis.

Protocols were developed for the examination of lower limb walking patterns in early rheumatoid arthritis using 3D motion capture. When the walking patterns of 18 early rheumatoid arthritis participants were compared to an age and gender matched control group, significant between-group differences in spatial-temporal parameters and joint movement patterns within the foot were observed. Walking speed in early rheumatoid arthritis participants was found to be significantly slower ($p<0.05$). This was accompanied by a delay in terminating stance ($p<0.05$). Principal component analysis showed that early rheumatoid arthritis participants exhibited a significantly greater ($p<0.05$) magnitude of eversion and abduction of the rearfoot and midfoot during gait. A significantly reduced ($p<0.05$) magnitude of dorsiflexion at the first metatarsophalangeal joint was also observed. Kinematic coupling relationships between the rearfoot and midfoot were also found to be significantly altered ($p<0.05$), suggesting that an additional source of mechanically based trauma is also present

within the foot. Linear regression analysis showed that these features were largely unexplained by current measures of disease activity and disease impact.

The findings of this research suggest that mechanically based foot pathology in early rheumatoid arthritis is of a greater magnitude than previously reported and that these changes are not explained by laboratory based measures of disease activity or patient-reported questionnaires. Based upon these findings, the multidisciplinary use of 3D motion capture is recommended to meet both current and future demands for the early assessment and targeted management of mechanically based foot pathology in early rheumatoid arthritis.

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List of Abbreviations, Acronyms and Nomenclature

Activities of Daily Living (ADL)

American College of Rheumatology (ACR)

American Rheumatology Association (ARA)

Arthritis and Musculoskeletal Alliance (ARMA)

Area Under the Curve (AUC)

British Society of Rheumatology (BSR)

Centimetres (cm)

Coefficient of Multiple Correlations (CMC)

Continuous Relative Phase (CoRP)

Coefficient of Variation (CV)

Clinical Health Assessment Questionnaire (CLINHAQ)

Disease Activity Score (DAS)

Disease Modifying Antirheumatic Drugs (DMARD)

Erythrocyte Sedimentation Rate (ESR)

European League Against Rheumatism (EULAR)

Ground Reaction Force (GRF)

Good Research Practice (GRP)

Health Assessment Questionnaire (HAQ)

International Classification of Functioning (ICF)

International Society of Biomechanics (ISB)

Intra-class Correlation Coefficient (ICC)

Joint Coordinate System (JCS)

Kilogram (Kg)

Kilopascal (kPa)

Leeds Foot Impact Scale (LFIS)

Limits of Agreement (LOA)

Medial Longitudinal Arch (MLA)

Medical Research Council (MRC)

Metres (M)

Metatarsophalangeal Joint (MPJ)

Midtarsal Joint (MTJ)

Millimetres (mm)

Modified Health Assessment Questionnaire (MHAQ)

Multi-dimensional Health Assessment Questionnaire (MDHAQ)

National Rheumatoid arthritis Society (NRAS)

National Health Service (NHS)

National Institute for Clinical Excellence (NICE)

Newtons (N)

North West Clinical Effectiveness Group for the Foot in Rheumatic Diseases (NWCEG)

Principal Component (PC)

Principal Components Analysis (PCA)

Primary Care Rheumatology Society (PCRS)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Research and Development (R&D)

Research Ethics Committee (REC)

Research Governance Framework (RGF)

Rheumatoid arthritis (RA)

Sharp/Van der Heidje Score (SHS)

Standard Deviation (SD)

Standard Error of Measurement (SEM)

Subtalar Joint (STJ)

Three-dimensional (3D)

Timed Up and Go (TUG)

Towards a Cure for Rheumatoid Arthritis (TACERA)

University Medical Centre Nijmegen (UMCN)

Visual Analogue Scale (VAS)

Variability of Continuous Relative Phase (VCoRP)

Variance Inflation Factor (VIF)

Chapter 1: Introduction

This chapter provides an introduction to the origins of the research questions and central hypotheses of this thesis. The novel elements of the research are summarised. A framework for the thesis structure and content is provided.

1.1 Research rationale

Early rheumatoid arthritis (RA) may be characterized by a pattern of rapidly progressive joint damage resulting in significant functional impairment within the first two years following initial diagnosis. Despite improvements in the management of early RA more than half of patients report walking impairments as a key consequence of this disease (Van der Leeden et al., 2008). Such impairments may be characterised by the adoption of antalgic gait patterns to reduce pain. Despite this, the extent and magnitude to which these adaptations take place within the lower limb is poorly understood.

Whilst there is a general consensus that lower limb physical impairment should be assessed in early RA, there is a lack of clarity as to how this should be undertaken. Currently no quantitative measure of lower limb biomechanical function is recommended by the National Institute for Clinical Excellence (NICE) for the evaluation of early RA (Nice, 2009). Although guidelines published by the North West Clinical Effectiveness Group for the Foot in Rheumatic Diseases (NWCEG) outline essential requirements for the musculoskeletal assessment of the foot and ankle in early RA, there are no specific recommendations concerning which musculoskeletal outcome measures to use (Combe, 2009). Whilst guidelines published by Woodburn et al., (2010) advocate the early screening and management of residual foot

pathology in RA, outcomes recommended for the assessment of the foot do not measure physical function directly. In the absence of validated outcome measures for use in the musculoskeletal assessment of the foot and lower limb in patients with early RA, clinical research has adopted 3D motion capture to provide data on spatial-temporal parameters, joint kinetics (those forces that cause movement) and joint kinematics (joint movement patterns independent of those forces that bring about this movement). It is from these definitions of 'biomechanical function' that this thesis will investigate the foot and lower limb in early RA.

Within these terms of reference, one 3D motion capture study has specifically investigated early RA foot function in a cross-sectional analysis of twelve patients within the first two years of disease onset (Turner et al., 2008). Using 3D motion capture to quantify foot movement patterns, this study reported that patients with early RA adopted slower self-selected walking speeds in which the foot exhibits motion patterns characteristic of the presence of excessive pronation. Owing to the small numbers of participants recruited for this study, the statistical significance of these findings was not reported. Likewise, whether these features were accompanied by concurrent modifications in hip and knee kinetics and kinematics was not investigated. Given that musculoskeletal impairments are a feature of early RA, there is a need to quantify and characterize early changes in lower limb biomechanical function in these patients. For this reason the first research question asked by this thesis is:

1. When people with early RA are compared to age and gender-matched healthy adults, are there significant between-group differences in the biomechanical function of the foot and lower limb during gait?

Rheumatology function tests are currently the only validated methods by which clinicians may assess and quantify physical impairment in early RA. Of these tests, the first two (grip strength and the ability of a patient to button and unbutton a shirt as quickly as possible: timed button test) are exclusively measures of upper extremity function. These tests are used as surrogate indicators of global physical capacity. Only one rheumatology function test assesses lower limb functional capacity; the timed assessment of self-selected walking speed. Whilst these tests are among the most reproducible measures used in clinical rheumatology, they are not designed to measure alterations in lower limb kinetics and kinematics that are associated with changes in gait in early RA. Given their use as proxy indicators of lower limb physical impairment, this thesis asks the following question:

2. Is there an association between the biomechanical function of the foot and lower limb in early RA with measures of rheumatology physical function?

In reality, the burdens of time mean that within the clinical setting functional capacity is more likely to be inferred from measurements of disease activity, than through the prescription of rheumatology function tests. Whilst a number of composite indices have been developed for use in rheumatology, disease activity is most commonly assessed using the Disease Assessment Score 28-joint count (DAS28) which combines the erythrocyte sedimentation rate (ESR) with a painful joint count of twenty eight sites within the body. Infrequently, measures of disease may also be supplemented with self-reported questionnaires assessing for the presence physical disability, most notably the Health Assessment Questionnaire (HAQ). Whilst acting as proxy indicators of lower limb function, measures of disease activity and self-reported physical impairment may have a limited capacity to detect early alterations in lower limb walking patterns. The DAS28 does not include an evaluation of the ankles and joints of the feet which are frequently involved in early RA. Likewise, the HAQ does not include a detailed assessment

of lower limb biomechanical function. The question as to whether such measures do indeed have a surrogate capacity to explain lower limb kinetics and kinematics in early disease has yet to be answered. With these limitations in mind, the third overarching research question asked within this thesis is:

3. Is there an association between the biomechanical function of the foot and lower limb in early RA with measures of disease activity?

In summary, the protocols developed and described within this thesis will extend current conceptual understanding of foot and lower limb biomechanical function in early RA by providing unique and comprehensive data. It is intended that the outcomes of this research will provide a more robust evidence basis upon which clinicians will evaluate and interpret lower limb movement strategies adopted by patients with early RA and thus inform optimal management of this population.

1.2 Overall Hypothesis

It is proposed that biomechanical function is significantly altered in the first two years following diagnosis of RA. From this, it is hypothesised that spatial-temporal parameters, joint kinetics and joint kinematics in adults with early RA will be significantly different from those of age and gender matched controls. It is also hypothesised that relationships will be found between altered biomechanical function in early RA and measures of disease activity and physical function.

1.3 Aims of the Research

The specific aims of this research are:

1. To establish reliable protocols for the biomechanical evaluation of the foot and lower limb in participants with early RA.

2. To compare baseline biomechanical function of the foot and lower limb in early RA participants compared to aged-matched healthy controls.

3. To explore the relationship between foot and lower limb biomechanical function and disease impact.

Aim 1. **To e*stablish reliable protocols for the biomechanical evaluation of the foot and lower limb in participants with early RA.***

To achieve this aim, protocols for the quantitative assessment of gait using 3D motion capture were developed. Protocols for the assessment of foot posture, rheumatology physical function and disease impact were also developed. To test whether protocols for the collection of quantitative 3D gait and foot posture data were robust, a repeatability study (Study 1) will be undertaken in two phases: Phase 1 will assess repeatability of measures prior to the start of the research. Phase 2 will investigate whether the repeatability of these protocols had remained robust until the end of the research.

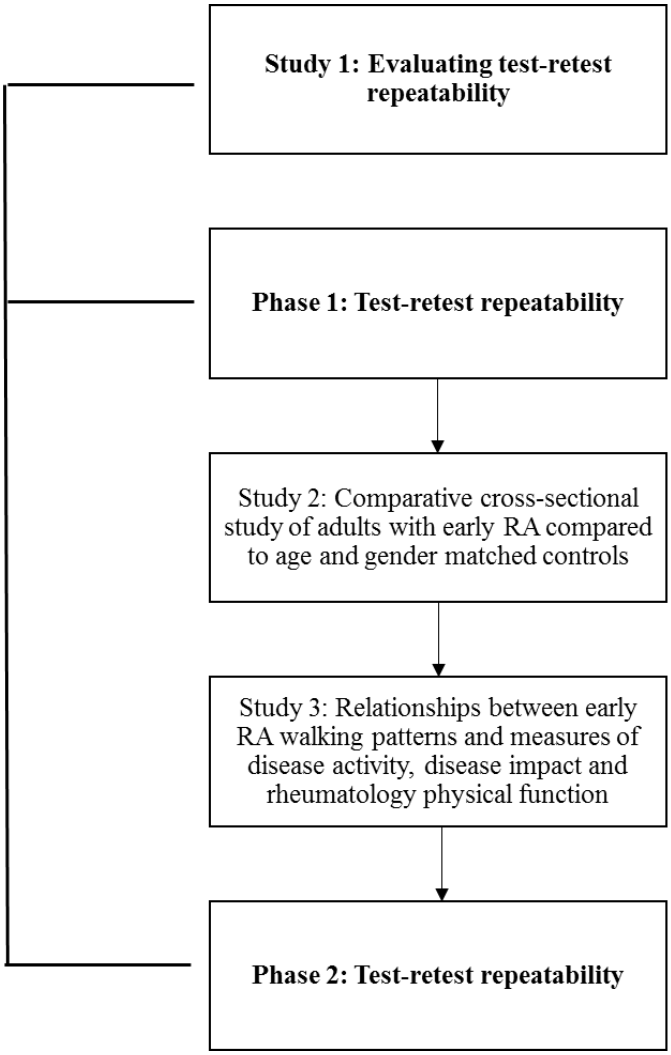

Figure 1.1: Flowchart illustrating the framework of study 1

Aim 2. To compare baseline biomechanical function of the foot and lower limb in early RA participants compared to age and gender-matched healthy controls.

Hypothesis 1 (H_1) - Lower limb spatial-temporal parameters in adults with early RA will be different from those of age and gender matched adults

Hypothesis 2 (H_2) - Hip, knee and ankle kinetics in adults with early RA will be different from those of age and gender matched adults

Hypothesis 3 (H_3) - Hip, knee, ankle and foot kinematics in adults with early RA will be different from those of age and gender matched adults

To achieve this aim and investigate these hypotheses, a comparative cross-sectional study (Study 2) will be undertaken. This study will use 3D motion capture to collect data on the spatial-temporal, kinetic and kinematic parameters of the foot and lower limb in participants with early RA. These data will be compared against a control group age and gender matched healthy participants. Data will be analysed using discrete variable analysis, principal component analysis and an investigation of inter-segmental coupling variability.

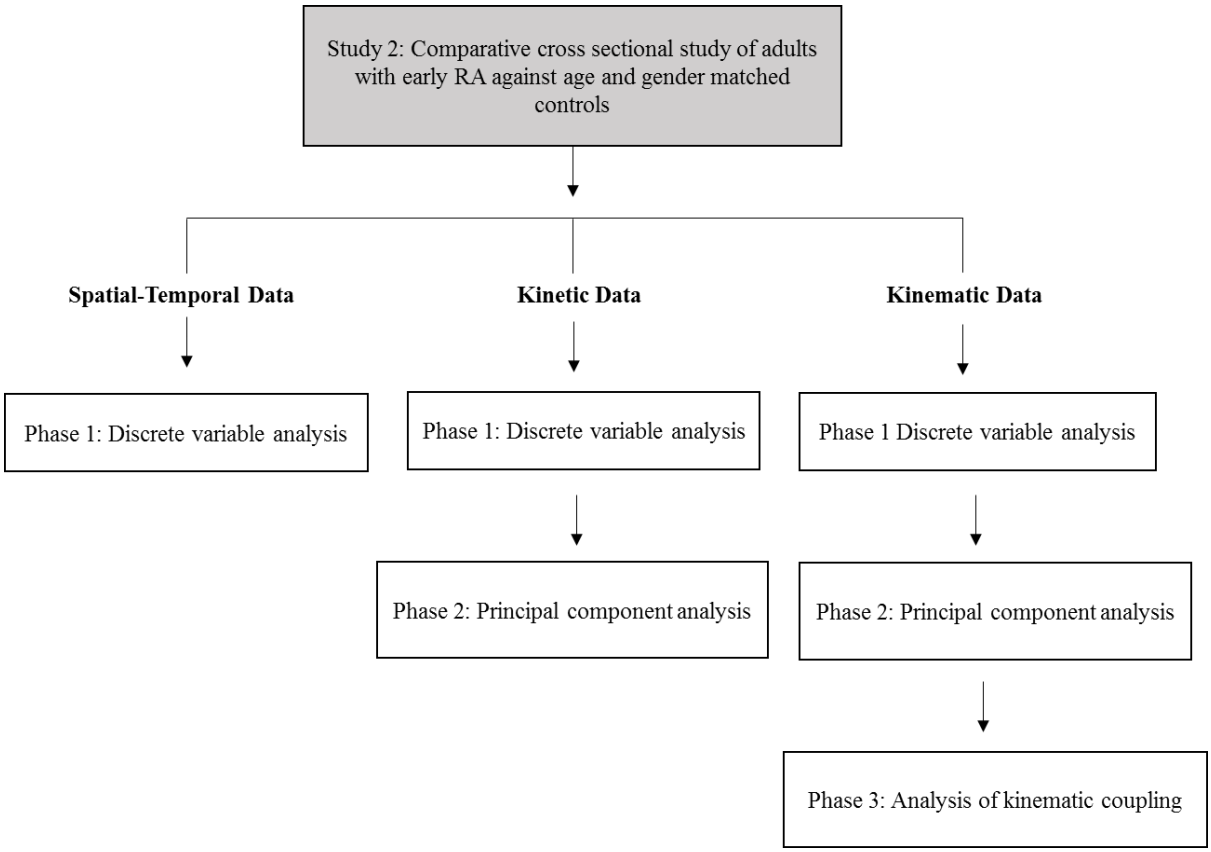

Figure 1.2: Flowchart illustrating the framework of study 2

Aim 3. To investigate the relationship between lower limb biomechanical function and disease impact.

Hypothesis 4 (H_4). - Relationships will be found between lower limb biomechanical function in early RA and measures of disease activity

Hypothesis 5 (H_5) - Relationships will be found between lower limb biomechanical function in early RA and measures of physical impairment

To achieve this aim and investigate these hypotheses, study 3 will analyse associations between lower limb biomechanical function in early RA and measures of rheumatology physical function, disease impact and disease activity. This will be investigated in two phases:

In phase 1, independent variables explaining lower limb biomechanical function in early RA will be identified using linear regression analysis. To assess between-group differences in these parameters an age and gender match control group will be recruited.

In phase 2, the relationship between these independent variables and foot kinematics will be investigated using linear regression analysis in a sub-group of early participants.

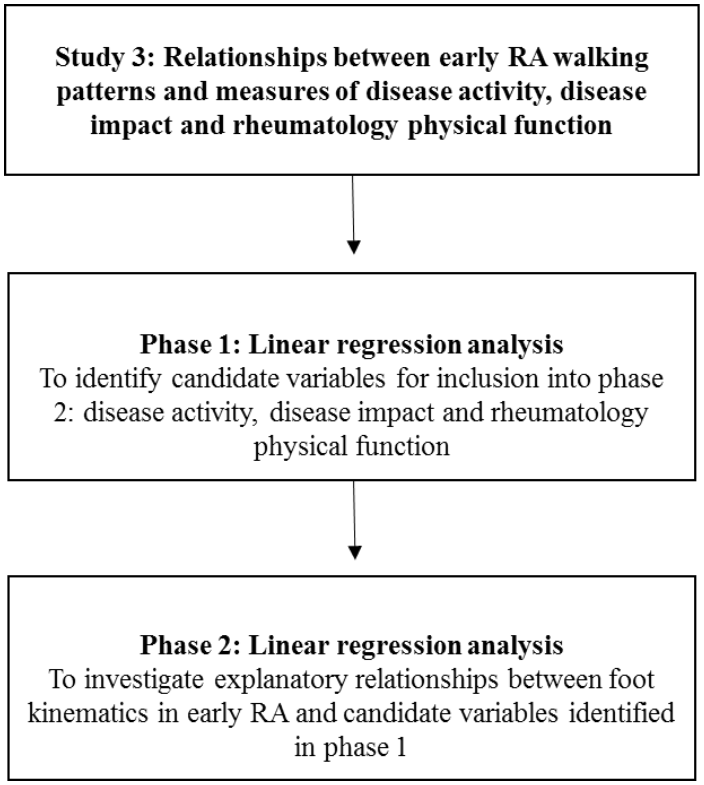

Figure 1.3: Flowchart illustrating the framework of study 2

1.4 Novel elements of this research

Previous studies have relied upon the analysis of a limited number of discrete variables to assess the repeatability of measures. In contrast to this, study 1 will incorporate a novel solution to this problem by using waveform symmetry analysis to allow kinematic waveform data to be assessed across all time points. To the best of the author's knowledge, this will be the first repeatability study of its kind to evaluate the shape, amplitude and excursion of these data using this technique.

Study 2 will be the first to use 3D motion capture to analyse the simultaneous movement patterns of the hip, knee, ankle and foot in early RA, determining the location and timing of

significant between-group differences in joint movement patterns and forces. It is believed that study 2 will be the first to investigate lower limb biomechanical function using principal component analysis and kinematic coupling.

In extending what is currently understood concerning the relationships between lower limb biomechanical function and measures of disease activity and disease impact, it is believed that study 3 will be unique in examining associations between lower limb kinematic data in early RA and measures of rheumatology physical function, disease impact and disease activity. To the best of the author's knowledge, this is the first study that will identify which explanatory variables significantly explain lower limb joint kinematics in early RA.

1.5 Thesis structure

Chapter 2 presents a review of the current literature, providing the background material used to generate of the aims and hypotheses of this research.

Chapter 3 presents the methodology of this research. Protocols are outlined for the use of 3D motion capture in assessing lower limb biomechanical function in early RA participants. Protocols for the application of rheumatology function tests and self-reported measures of disease impact are given. The statistical analyses used in this research are outlined.

Chapter 4 presents the findings of study 1. To test whether the protocols developed for this research were robust, an analysis of the repeatability of 3D motion capture and foot posture assessment are undertaken.

Chapter 5 presents the findings of study 2 (phases 1 and 2). This is a comparative cross sectional analysis of 18 early RA participants compared to an age and gender matched control group. Between-group comparisons of spatial-temporal, kinetic and kinematic data are presented and significant findings reported.

Chapter 6 presents the findings of study 2 (phase 3), determining whether intersegmental coupling patterns in early RA are significantly altered in the presence of early RA. The findings of this analysis are reported in this chapter.

Chapter 7 presents the results of study 3. In this study the relationship between foot kinematics in early RA and current measures of disease activity and physical impairment are analysed in two groups of early RA participants. This chapter reports the results of this study.

Chapter 8 presents a summary discussion of the key findings of this research. Specific consideration is given to the limitations of the research, its clinical interpretation and proposals for future research.

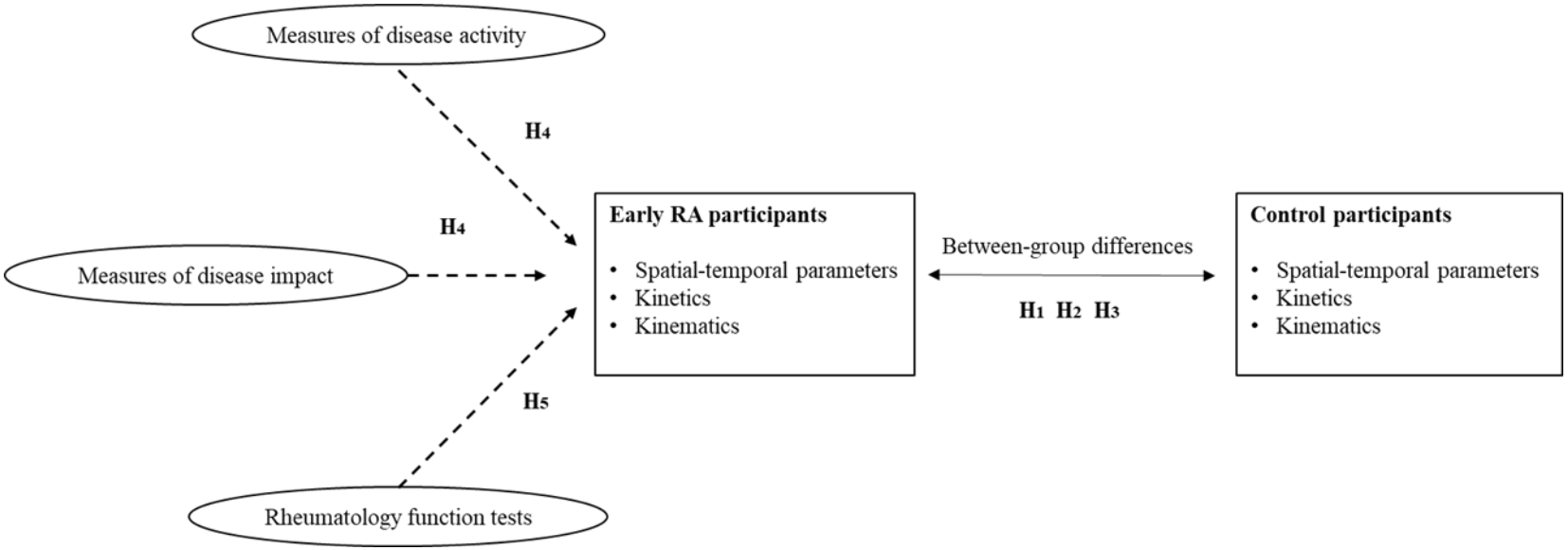

Figure 1.4: Conceptual framework of thesis

Chapter 2: Literature Review

This chapter reviews the relevant literature on the clinical features of what is termed early RA. Current limitations in the evaluation of foot and lower limb pathomechanical function in early RA using 3D motion capture are discussed. A justification for this research is then presented.

2.1 Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram represented in figure 2.1 depicts the flow of studies used in the compilation of this literature review of the biomechanical function of the foot and lower limb in early RA. The following search terms were used: early rheumatoid arthritis, spatial-temporal, kinetics, kinematics, hip, knee, ankle and foot.

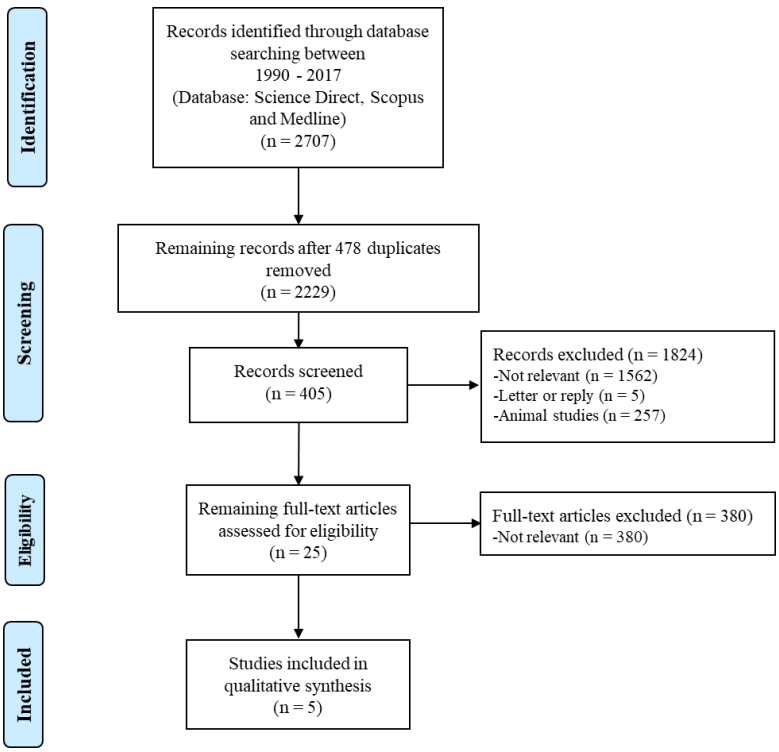

Figure 2.1: PRISMA flow diagram of search strategy

2.2 Early RA

This section explains the prevalence and frequency of early RA in the foot and lower limb, identifying current limitations in the clinical assessment of musculoskeletal function associated with this disease.

2.2.1 Prevalence

Early RA is defined by the presence of disease activity of less than two years duration (Emery et al., 2014). Data from the National Institute for Health and Care Excellence (NICE) show that approximately 12,000 new cases are diagnosed annually, resulting in a prevalence rate for this disease of 0.8% (NICE, 2009). Early RA is significantly higher in women at 1.16%, compared to 0.4 % in men (Nikiphorou et al., 2016). Its impact upon the UK economy is significant both in terms of direct costs to the National Health Service (NHS) and indirect costs such as early mortality and reduced productivity. Indeed, approximately one third of patients stop work within two years of diagnosis, resulting in a total cost to the UK economy of between £3.8 and £4.75 billion per year (NICE, 2009).

2.2.2 Clinical features

Early RA is characterised by a persistent and destructive polyarthritis. This is accompanied by a progressive spread from small to large joints, which is often associated with the presence rheumatoid factor and/or anti-cyclic citrulinated peptide (Singh et al., 2015). Small joint inflammation in the lower limb is a hallmark of early RA, although the site of initial presentation may vary – knee: 8%; foot: 13% and ankle: 6% (Combe, 2009). Variability in its clinical presentation means that the pattern of disease may be either monoarticular or

polyarticular at initial onset, with joint damage ranging from mild cartilage degradation to rapidly progressive erosive disease. An additional defining feature of early RA is a disease course that may be either cyclic or unrelenting (Emery and Symmons, 1997; van Zeeben et al., 1994; Wolf, 1996). A variable combination of these characteristics produces a broad heterogeneity that is in part manifested in differences in disease outcomes ranging from remission to severe disability and premature mortality (Emery et al., 2014).

2.2.3 Disease Classification

The necessity of basing the diagnosis of RA upon the pattern of clinical and investigational findings, means that the clinical recognition of RA within the earliest stages of the disease remains a key diagnostic challenge (Dale, 2010). As the pattern of clinical features develop over time, it is disease chronicity which is a key pathological feature (Singh et al., 2015). For this reason, American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria presented in table 2.1 also require clinical features to be present for at least six weeks (Aletaha et al., 2010).

2.2.4 Pharmacotherapy

As structural damage associated with early disease cannot be reversed, pharmacotherapy is the cornerstone of treatment in early RA (Aletaha and Smolen, 2011). Advancements in the management of early RA have seen a gradual shift away from an escalated, or conventional *step-up* approach to pharmacotherapy, in favour of one in which *treat to target* is the primary aim. This approach incorporates stringent disease control combined with the aim of achieving a predefined level of low disease activity, or ideally, remission within the first two years.

NICE guidelines recommend the early use of Methotrexate as first-line therapy as an "anchor drug" combined with a second disease-modifying antirheumatic drugs (DMARD) plus the use of short term glucocorticoids, tapering the most toxic drug first and maintaining the DMARD with the best efficacy/toxicity ratio for as long as required (NICE, 2009). Histologically, the period of transition between immune plasticity and immune rigidity coincides with pannus formation and erosive joint damage. At this point, therapeutic interventions have the capability to fundamentally alter the disease course and hence the disease prognosis (Luqmani et al., 2006). Beyond this *"window of opportunity"*, a predictable course of abnormal inflammation and immune dysfunction develops which is less responsive to immunomodulatory therapy (Blom and Riel, 2007).

Table 2.1: 2010 ACR-EULAR classification criteria for early RA

Joint Involvement	***Score***
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4 -10 small joints	3
>10 joints (at least 1 small joint)	5
Serology	
Negative RF positive ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high positive ACPA	3
Acute Phase Reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of Symptoms	
<6 weeks	0
≥6 weeks	1
Score of ≥6/10 is needed for classification of definite RA	

2.2.5 Radiographic progression

Data on the rate of radiographic progression in early disease is not unanimous. Radiographic progression in early RA has variously been described as approximately linear, fast-slow, slow-fast and sigmoid (Hulsmans et al., 2000; Plant et al., 1998; Dixey et al., 2004; Graudal et al., 1998). In fact, the severity of radiological changes and erosion rates within the first year of disease vary considerably. The majority of early RA patients develop structural damage within the first two years of disease. Significant radiographic progression was reported in patients within the first twelve months by Fautrel and colleagues who noted that 32% of all patients treated with conventional DMARD therapy demonstrated evidence of disease progression defined by a mean change of 1.6 ± 5.5 on the modified Sharp/Van der Heidje score (SHS). Of these, rapid radiological progression, defined as structural damage of at least 5 points on the SHS, was noted in 11% of patients irrespective of baseline risk factors (Fautrel et al., 2012).

2.2.6 Outcomes in early RA

With clear guidelines on the classification of early disease, the question arises as to whether the early recognition and management of RA has improved outcomes for patients? This depends upon how outcomes are measured. Where management is commenced in the first three months following disease onset, 50% of patients achieve medically managed remission compared with 15% where the onset of treatment is delayed (Deighton et al., 2010). There are of course consequences arising from a delay in instituting a diagnosis. A study by Rat et al., (2004) reported a 73% risk of establishing erosive disease prior to the onset of treatment where treatment is delayed by more than twelve months. Despite the clear benefits of early treatment, the mean duration of time between the onset of synovitis and commencement of therapy remains in excess of 6 months (Sorensen et al., 2015).

If the early recognition and management of this disease has so far proven to be clinically challenging, the question arises as to whether improvements in the management of early RA have led to a reduction in the physical impairment seen in patients living with this condition? The following sections discuss this aspect with specific focus on the foot and lower limb.

2.2.7 Physical impairment in early RA

Whilst achieving the complete remission of disease activity is now seen as a realistic objective in the management of early RA, sustained remission may be unachievable (Deighton et al., 2010). In practice, routine clinical and laboratory examinations incorporated within composite indices also appear to lack sufficient sensitivity to assess remission according to this definition (Balsa et al., 2010). Ultrasound investigations of both early and established DMARD treated RA have demonstrated the presence of on-going synovitis in the presence of DAS28 defined remission, suggesting that remission according to current clinical indices may not necessarily be accompanied by the complete suppression of disease activity (Brahe et al., 2016; Dale et al., 2016; Moller et al., 2017; Mouterde et al., 217). This may therefore be a factor underlying previous observations that despite improvements in pharmacotherapy, walking impairments remain a key feature of early disease (Van der Leeden., 2008; Otter et al., 2010).

2.2.8 Early foot involvement in RA

A key characteristic determining the manner in which walking impairments manifest is the high frequency of foot pathologies seen in early RA. In 63 early RA participants recruited through the National Rheumatoid Arthritis Society (NRAS), Otter et al., (2010) found that the frequency of foot pain within the first two years following symptom onset reached 90.5%

despite DMARD therapy. Similar findings were also seen in hospital recruited participants (88.2%). When anatomical location was taken into account, this group reported that the frequency of pain was found to be greatest at the forefoot (63.3%). A high frequency of pain was also reported at the ankle in 42% of participants whilst the rearfoot was affected in 21.8%. Though the frequency of pain was found to be least at the midfoot, this was still reported in 17% of participants (Otter et al., 2010).

2.2.9 Joint involvement patterns within the foot in early RA

Disease of the forefoot is the first manifestation of RA in 15% of patients (Trieb et al., 2013). The presentation of disease related structural damage within the forefoot appears to follow a characteristic pattern of joint involvement. Ultrasound analysis of 31 DMARD treated patients by Bowen et al., (2010) found early evidence of synovial hypertrophy at the fifth metatarsal in around 74% of patients. Around 58% of these patients also exhibited similar changes at the second metatarsal. This group also found erosion rates at the first metatarsal to be high, reaching 75%. This was observed to be far greater than that seen at second metatarsal (9.7%). By contrast, active metatarsophalangeal joint (MPJ) synovitis was found to be less prevalent, ranging from 9.7% to 3.2% for the fifth and second MPJ respectively (Bowen et al., 2010). In an magnetic resonance imaging (MRI) study of 24 patients, Siddle et al., (2012) reported pathological changes to be present in all of the lesser metatarsals. This group found the fifth MPJ to be the most commonly affected site in the forefoot with bone oedema and erosions affecting between 92% and 50% of participants depending upon site and pathogenic process. Localised plantar plate pathology at the lesser metatarsals was associated with MRI located synovitis 71%, bone oedema 71% and erosions 71%.

In a follow up study, Siddle and colleagues speculated that the prevalence of early pathological changes within the forefoot are under the influence of factors such as altered foot kinematics, possibility acting in conjunction with inflammatory pathophysiology and structural changes affecting the plantar plate mechanism to determine the severity of changes (Siddle et al., 2014). In this study, bone erosions favoured a distribution pattern that was predominantly plantar-medial and plantar-lateral in nature, affecting primarily the fifth metatarsal. These changes were found to co-exist with reductions in plantar pressure, ranging from 581.5kPa ± 379.6 at the first MPJ to 355.2kPa ± 242.0 at the fifth. This was felt by this group to indicate the presence of pathomechanical modifications to gait in response to early disease.

Within the foot, clinical observations have indicated that synovitis may deteriorate over time, responding to interventional pharmacology at a much slower rate than markers of disease state would indicate. Observations of soft tissue pathology suggest that synovitis may be initiated by the pathological processes that are active in early RA but then perpetuated independently by mechanical trauma (Bowen et al., 2010). Little is known of the role of foot pathology in relation to walking impairments in early RA. Investigating this mechanical component of early disease therefore warrants further investigation.

2.2.10 Frequency of lower limb involvement in early RA

Reflecting the propensity of early RA to affect multiple joint sites within the lower limb, Grondal et al., (2008) found that concurrent involvement of the forefoot and knee was seen in 14% of patients. An additional 9% of patients also found to experience combined hindfoot-ankle-knee involvement (Grondal et al., 2008). Where more than one joint is involved a median

of 3 joints are affected with concurrent involvement of the foot, hand and shoulder being the most frequently seen combination in 47% of cases. This is followed by foot, hand and knee involvement which was seen in 45% of patients (Grondal et al., 2008). Given the high prevalence of walking impairments in early disease, whether these arise primarily from active foot disease or from the simultaneous pathomechanical function across multiple joint sites is unclear. Understanding where within the foot and lower limb functional impairments first arise would allow more targeted assessments and interventions to be undertaken in early RA.

2.2.11 Walking impairments in early RA

In an attempt to reposition joints to lessen symptoms, patients with early RA adopt antalgic gait patterns. For this reason, active foot disease is considered the primary cause of walking impairments in early RA. A study by Van der Leeden and colleagues of 848 DMARD treated patients found the prevalence of walking impairments to be around 56.7% within the first two years following diagnosis. Of these 32% of patients described their disability as mild, 20% as moderate and 4% as severe (Van der Leeden et al., 2008). The assessment and management of altered 'function' in early disease is recommended in rheumatology core set guidelines by Woodburn et al., (2010). However, little appears to be known of the simultaneous joint movement strategies that facilitate antalgic gait patterns adopted in early RA. Evaluating the location and magnitude of these early alterations in joint movement patterns within both the foot and lower limb may help elucidate the pathomechanical origins of early physical impairment. Yet, assessing altered joint movement patterns is difficult, in part due to the complex anatomy of the foot and lower limb and the limitations of current measurement protocols (Jarvis et al., 2013).

2.2.12 Limitations in assessing lower limb biomechanical impairment in early RA

Currently no quantitative measure of lower limb biomechanical function is recommended for the evaluation of early RA in guidelines published by NICE (NICE, 2009). Though guidelines published by NWCEG outline essential requirements for foot and ankle assessment, there are no specific guidelines set out for the musculoskeletal assessment of the foot and lower limb (Williams et al., 2011). Furthermore, whilst guidelines published by Woodburn et al., (2010) advocate the early screening and management of residual foot pathology in RA, candidate outcomes recommended by this group for the assessment of the residual foot pathology do not measure physical function directly.

Compounding this, current paradigms of musculoskeletal assessment are unsuitable for use in the assessment of physical impairment in earl RA. A central paradigm that still underpins clinical practice is that of Root and colleagues (Root et al., 1977). However, the clinical assessment techniques attributed to this group have been found to poorly correlate to foot kinematics during gait (Nester., 2009; Jarvis et al., 2017). As clinical assessments of musculoskeletal pathology are often largely based upon observation rather than objective measurement, a paucity of evidence currently informs the clinical recognition and management of musculoskeletal conditions (Jarvis et al., 2017). In the absence of validated outcome measures for use in the musculoskeletal assessment of the lower limb in patients with early disease, clinical research has adopted 3D motion capture to provide data on spatial-temporal parameters, joint kinetics and joint kinematics.

2.3 Evidencing lower limb functional impairment using 3D motion capture

The following sections discuss the application and limitations of 3D motion capture in the study of biomechanical function in early RA.

2.3.1 3D Motion Capture

It is assumed that 3D motion capture mitigates against current conceptual limitations by providing a reliable and objective measurement of musculoskeletal status (McGinley et al., 2013). Furthermore, the magnitude of error reported in 3D motion capture data is considered compatible with that of clinical decision making (Schwartz et al., 2004). As it is not theoretically embedded within current paradigms of musculoskeletal assessment, the pathomechanics and symptomology of the foot and lower limb may instead be explained though the analysis of *kinetics* and *kinematics*. Kinematics refers to joint movement patterns adopted by individuals, independent of those forces that cause movement. Kinetics refers to those forces that result in movement, be they internal (due to muscle contraction) or external (due to gravity). Data on these parameters therefore provide information on what causes movement of the lower limb to take place (Capozzo et al., 2005). It is within these definitions of *biomechanical function* that investigators have studied the impact of early RA on the foot and lower limb.

2.3.2 Biomechanical modelling in 3D motion capture

In 3D motion capture, biomechanical models have been used to represent the foot as a system of rigid segments, each defining a specific anatomical structure (Rankine et al., 2008). Movement between adjacent segments characterise joint rotation patterns (Capozzo et al.,

2005). Whilst early studies of foot kinematics in RA represented the foot as a single rigid segment, variability in marker placement in the presence of deformity resulted in errors in data in excess of 6° (Davis et al., 2008). With the need to provide more reliable and comprehensive data, a number of multisegment foot models have been described in the literature. The number of segmental definitions in these models vary, from two segments (Kepple et al., 1990; Mosely et al., 1996), three segments (Hunt et al., 2001; Davis et al., 2008), four segments (Cornwall and McPoil, 2002; Myers et al., 2004; Kidder et al., 1996; Carsen et al., 2001), five segments (Kitaoka et al., 2006; Tome et al., 2006; Jenkyn et al., 2007), six segments (Jenkyn and Nicol, 2001; Leardini et al., 1999; Tome et al., 2006), seven segments (Hyslop et al., 2010) and nine segments (Hwang et al., 2004; McWilliams et al., 2003).

2.3.3 Biomechanical models used in early RA research

Of the aforementioned multisegment models, those described by Carsen et al., (2001), Kidder et al., (1996) and Hyslop et al., (2010) have been applied to participants presenting with early RA (Turner et al., 2006; Khazzam et al., 2006; Barn et al., 2013; Gibson et al., 2014). Differences in the calculation of segmental rotations between these foot models makes comparability between studies difficult (Rankine et al., 2008). Two of these models (Carsen et al., 2001; Hyslop et al., 2010) use the Joint Coordinate System (JCS) outlined by Grood and Suntay (1983). Segmental rotations are therefore calculated about an orthogonally located floating axis. By contrast, the model described by Kidder et al., (1996) uses a joint projection angle technique described by Simon et al., (2006). Differences in these conventions have been shown to result in discrepancies in the calculation of segmental rotations by up to 5° in the frontal and transverse plane (Cappozzo et al., 2005).

2.3.4 Statistical approaches to data analysis in early RA research

In describing the kinematics of the foot in early RA using 3D motion capture, several challenges have faced investigators. Foremost among these is that the pathological processes affecting tendon, soft tissue and bone may spontaneously give rise to a variable combination of non-random, structured movement patterns. Together, these give rise to the concept of *physiological complexity* (Manor et al., 2010). In attempting to measure physiological complexity, investigators have historically viewed these data as the consequence of deterministic motor behaviours which are both predictable and the product of linear correlations between data (Van Emmerick et al., 2016).

Reflecting this deterministic approach to data analysis, foot kinematics in early RA have so far been reported using the mean and standard deviation of angular rotations at predetermined gait cycle events (or discrete variables) derived from conventional descriptions of the gait cycle by Perry, (1992). These discrete variables have varied across studies, focusing on the use of data at initial contact (Turner et al., 2006), toe-off (Turner et al., 2006), mean angular rotations (Turner et al., 2006; Barn et al., 2013; Gibson 2014) and the total range of motion (Khazzam et a., 2006). A limitation of this approach is that historically the pathomechanical significance of these events have been viewed as arbitrary (Schwartz et al., 2012). Furthermore, the analysis of discrete variables does not provide data on the duration of gait over which altered segmental kinematics deviate from that considered normal (Cimolin and Galli., 2014). Given that kinematic data incorporate this temporal component, this may be problematic; waveform data exhibit contractions and dilatations which serve to amplify or diminish between-group differences beyond these predetermined discrete variables (Schwartz et al., 2012).

Accompanying these sigmoidal fluctuations in kinematic waveforms, variance in these data is viewed as an intrinsic feature of gait (McGinley et al., 2013). Studies of early RA have expressed such cycle-to-cycle variability using the statistical concept of variance (Field, 2009). Whilst this acknowledges that the rhythmic movement patterns seen in early RA kinematics may be both stable and variable, reporting early RA kinematics in this manner does not take into account the presence of randomness and stochasticity within these movement patterns (Riley and Turvey., 2002). With sample sizes ranging from 10 early RA participants (Barn et al., 2013) to 15 (Gibson et al., 2014), it is also uncertain as to whether between-group comparisons with healthy controls are free of type II error (Portney and Watkins, 2009).

2.3.5 Alternatives to discrete variable analysis in early RA

Alternatives to discrete variable analysis have been limited. In mitigating against the limitations of discrete variable analysis, investigators have instead used the coefficient of multiple correlation (CMC) to examine gait between-subject variance across the full duration of gait (Gibson et al., 2014). This approach is still problematic. Roislien et al., (2012) found that the CMC is affected by signal-to-noise ratio, so that small ranges of motion may compromise the amplitude of waveform data relative to measurement error and natural variation. As a result, erroneously low CMC values may be computed. An additional observation was that the CMC does not adjust for a high correlation that may exist between data points that make up a gait waveform. This again may lead to misleadingly low CMC values. Roislien and colleagues concluded that as an objective measure the CMC should not be used in its current form. In elucidating the impact of early RA on foot kinematics, finding an alternative to the CMC is therefore an aspect that warrants further investigation (Roislien et al., 2012).

Current methods of measuring and describing altered foot motion in early RA may not adequately take into account physiological complexity in altering movement patterns. It is plausible that the true magnitude, location and timing of altered foot kinematics in early RA have yet to be fully clarified. To elucidate such data, an alternative statistical technique to the CMC is required. In advancing current understanding of the nature of mechanically based trauma within the foot and lower limb, this is an aspect that warrants further investigation.

2.3.6 Early RA foot kinematics

This section discusses what has so far been published on the impact of early RA upon on the kinematics of the rearfoot, forefoot, first MPJ, knee and hip.

2.3.7 The rearfoot

A long term consequence of RA on the foot is the pathogenesis of pes planovalgus (Turner et al., 2006). The role of rearfoot kinematics in the early onset of pathomechanical function has therefore been of particular interest to investigators. Woodburn et al., (2002) found that the kinematics of the rearfoot become altered even in the presence of moderate disease activity (DAS = 3.4 ± 1.2), low-to-moderate functional impairment (HAQ = 1.00 (0.47, 1.75) and low levels of radiographic damage (Larsen index of feet was 5.5 (0, 13.8). The rearfoot was observed to operate within an everted and internally rotated envelope, with peak eversion increasing by 6.8°, reaching a maximum of -10.6° ± 5.4°. This was accompanied by an increase in internal rotation of the rearfoot of 4.8°. Although the timing and duration of these features have yet to be elucidated, similar observations were made in a cross-sectional study by Turner et al., (2006). Reporting on the segmental kinetics and kinematics in a group of twelve patients

within the first two years following symptom onset, this group noted that moderate disease activity (DAS28 <3.2) modulated by both conventional and biological therapies, did not protect against the onset of pathomechanical function. Peak rearfoot eversion was found to reach -5.5° ± 9.8°, 20% greater than that seen in controls. These changes were also accompanied by a greater magnitude of dorsiflexion at the initial contact, evidenced by an increase in foot contact angle of 14.2° ± 4.5° in early RA patients compared with 13.8° ± 2.4°seen in controls.

Whilst rearfoot alignment is altered in early RA, the total range of frontal plane motion appears not. Woodburn et al., (2002) found this to be reduced by 0.9°, whilst differences in sagittal plane motion were not found to be non-clinically relevant, exhibiting only a 2.1° between-group difference. With the relative preservation of motion, this may explain why rearfoot malalignment has been shown to be reducible within the first two years of diagnosis. When personalised orthoses are prescribed, peak rearfoot eversion has been shown to reduce to between -1.8° and -2.2° (Gibson et al., 2014). This raises the possibility that additional data on the timing, magnitude and duration of theses changes may help in the enhance targeting of such interventions.

2.3.8 The midfoot

There is limited published data on the kinematics of the midfoot in early RA. Investigating the contribution of rearfoot malalignment to the pathogenesis of long term functional outcomes is technically challenging. Three-dimensional foot models rely on the use of the palpable anatomical landmarks to define joint axes and track movement patterns (Cappozzo et al., 2005). Where these landmarks are absent or where specific bones are inaccessible, it is not possible

to model structures such as the midtarsal joint with an acceptable level of precision (Deschamps et al., 2012). With the exception of the multisegment foot model described by Hyslop et al., 2010, none of the models so far used in early RA research have included a segmental definition of the midfoot. Whilst the foot model described by Hysop et al., (2010) defines the midfoot segment, its kinematics were not described by Gibson et al., (2014) owing to the limitations of in-shoe measurement of midfoot kinematics.

In the presence of early RA, the sagittal plane excursion of the navicular has been used as a proxy of midfoot kinematics (Turner et al., 2006; Gibson et al., 2014). Turner and colleagues observed that where increased rearfoot eversion is present, peak medial longitudinal arch (MLA) height reduces by 8% (Turner et al., 2006). In a study of 10 participants in the first three years of diagnosis, Barn et al., (2013) also reported midfoot collapse in association with rearfoot pathology. This group noted that whilst the percentage of maximum isometric contraction of tibialis posterior, expressed as a median and interquartile range, was found to be increased at initial contact (RA group, 48% (35 – 116); Control group, 22 (14-28)), this was insufficient in preventing pathomechanical alterations, characterised by a reduction in navicular height of 71% (RA group, 29mm ± 9 compared; Control group, 41mm ± 0.1).

Whilst corroborating clinical observations of the pathomechanical inter-relationship between rearfoot and midfoot kinematics, these data do not fully elucidate the complexity of coordinated movement between these segments. Given that end stage functional impairment in RA historically been reported to be associated with the decoupling of motion between the shank, rearfoot and midfoot within six years of diagnosis (Woodburn et al., 1999). Investigating the coupling of motion between these two segments in early RA warrants further investigation,

especially as altered function at these sites has been shown to be amenable to early intervention (Gibson et al., 2014).

2.3.9 The forefoot

Three-dimensional motion capture studies do not include data on forefoot kinematics in early RA. This contrasts to established disease where RA participants may eventually exhibit an overall reduction of motion in all three cardinal body planes of up to 3.1°. The largest between-group differences have been reported for peak plantarflexion which has been shown to be reduced by 4.1° (Woodburn et al., 2004). Turner et al., (2008) found that regardless of where primary deformity is located, a decrease in the range of motion at the forefoot of more than 9° may be seen when compared to healthy controls.

These data should be treated with caution. The forefoot is highly deformable and kinematic data, particularly that of the first metatarsal, have been found to violate assumptions of rigid body modelling; a major factor determining error in 3D motion capture data. A study by Nester et al., (2014) tracking the motion of intra-cortical bone pins, reported that displacement of the first metatarsal to range from 1.6° to -3.9° in the frontal plane and from 2.9° to -5.4° in the transverse plane.

Analysing the simulated gait in ten cadavers Okita et al., (2009) observed significant differences in motion between skin mounted markers and intra-cortical bone pins. This group found that transverse plane motion of intra-cortical pins was particularly susceptible to error, leading to errors in measurement of 4.1° in transverse plane rotations of the first metatarsal.

Skin motion artefact between intra-cortical bone pins and surface mounted markers was also found to range between 3.4° and 3.7°. Given that the acceptable level of absolute error in 3D motion capture is considered to be 5° (McGinley et al., 2013), this calls into question the utility of investigating forefoot motion using rigid body modelling (Okita et al., 2009).

2.3.10 The first metatarsophalangeal joint

Participants with early RA have been shown to exhibit a reduced range of dorsiflexion at the first MPJ by up to 12.9° (Khazzam et al., 2006). Whether this also corresponds to a decrease in both the foot elevation angle at terminal stance (RA, -82.2 ± 2.0; Control, -69.1 ± 13.5) and plantarflexion moment of gastrocnemius and soleus of -1.5 ± 0.1 Nm/kg reported by Turner et al., (2006) is uncertain. Investigating the relationship between these motion patterns may further elucidate the adaptive that processes take place in early RA gait. Localised synovitis and erosion at the first MPJ has been shown to demonstrate a strong negative correlation coefficient to maximum dorsiflexion (95% CI -0.8, -0.3) (Dubbledam et al., 2011). Alterations of this nature are thought to act as an adaptation process, limiting compressive forces applied to the joints of the forefoot and thereby reducing pain to the forefoot (Laroche et al., 2005). The mechanical consequence of which is thought to shift the plantar aspect of the foot posterior to the centre of pressure resulting in a smaller ankle plantarflexion torque and leg acceleration into the following swing phase (Neptune., 2001). The relationship between changes in adaptive kinematics at the first MPJ and those seen elsewhere within the lower limb have yet to be investigated in early RA.

2.3.11 The knee

In early RA, contemporary data on the impact of early RA on knee kinematics is lacking. In established disease electromyography has previously suggested a link between pathomenchanical function of the foot and that of the knee. Woodburn and colleagues conjectured that valgus deformity of the rearfoot in excess of -13.7°± 4.9 may be accompanied by a reduced motor strength in gastrocnemius, soleus and tibialis posterior as reported by Keenen et al., (1991) in a study of established RA. This causal relationship appears not have been given serious attention. It is possible that a deceleration of the forward advancement of the tibia associated with adaptive mechanics may result in an increased valgus alignment and tissue stress at the knee as suggested by (Woodburn et al., 1999). Since that study, there appears to be limited published research investigating the inter-relationship of between the kinematics of the foot and those of the hip and knee, especially in early RA. With total joint replacements of the knee reported to be 49.4% of patients (Nikiphorou et al., 2014), investigating this aspect further may provide novel data on the possible role of altered foot function in mechanically based trauma to the knee in early RA. With that knowledge, interventions may be targeted towards improving foot function.

2.3.12 The hip

Data on hip kinematics in RA are also scarce. In particular, the impact of antalgic gait patterns on hip kinematics in early RA may be an important omission. Once established, RA may result in limitations in motion at this joint. Reporting on sagittal plane data, Weiss et al., (2008) studied lower limb joint movement patterns in fifty pre-operative participants with a mean disease duration of seventeen years presenting with moderate self-reported physical impairment (HAQ = 1.03 ± 0.66). Using the conventional lower limb model described by Davis

et al., (1991) this group observed that when participants exhibit a reduced walking velocity of 0.96m/s ± 0.32, the total range of hip motion may be reduced by up to 14° in conjunction with a reduced range of abduction of up to 4°. Importantly, these changes were found to occur in conjunction with a reduction in ankle plantarflexion of 10°. With the development of antalgic gait patterns seen as a key feature of physical impairment in early RA (Carroll et al., 2015), this raises the possibility that such impairments in function may be established early, arising from the interaction between altered segmental kinetics and kinematics at the foot, ankle, knee and hip. Identifying and measuring alterations of this nature may allow a greater targeting of interventions to be provided at an earlier point within the natural history of the disease.

2.3.13 Future directions

It may be argued that accounts of pathomechanical function in early RA have been based upon the premise that these exhibit deterministic behaviour patterns. This may not take into account the complex interrelationship between the main functional components of the foot and lower limb acting under the combined influence of mechanical and pathophysiological processes (Van Emmerick et al., 2016). To extend what is currently understood of the pathomechanical function of the foot and lower limb in early RA, adopting novel statistical approaches may be necessary in providing unique data elucidating pathomechanical relationships between the main functional components of the foot and lower limb.

In finding alternatives to the use of discrete variable analysis, one approach may be to recognise that the biological impact of early RA on human tissue may result in segmental kinematics that exhibit non-linear behaviours under the influence of more than one independent variable

(Van Emmerick et al., 2016). This implies that the kinematics in early RA may be impacted upon by the external effects of both deterministic and random processes associated within the pathophysiology of the disease (Riley and Turvey, 2002). For investigators studying the impact of early RA on foot kinematics, this may have important implications for the way in which these data are analysed and interpreted. It is plausible that in early RA, non-linear behaviour in foot kinematics operate within what is termed a '*dynamical system'* (Van Emmerick et al., 2016). Reflecting the impact of physiological complexity, this approach acknowledges that movement behaviours may evolve over time, whether they occur within a steady state or are in a period of change (Beck, 1995). The issue of how altered kinematics in early RA are measured therefore becomes important.

In a dynamical system, physiological complexity and non-linear behaviour manifest in the form of kinematic variability. This arises from the independent contributions of the soft tissue and osseous components of the foot which allow motor tasks such as gait to be performed using different degrees of freedom (Riley and Turvey., 2002). Within a dynamical system, variability is measured through the coordinated (or coupled) motion that takes place *between* segments (Stergiou et al., 2001). This represents a fundamentally different conceptual approach to that previously undertaken in studies of early RA (Turner et al., 2006; Khazzam et al., 2006; Barn et al., 2013; Gibson et al., 2014).

In moving forward, analysing intersegmental coupling may offer an adjunct to conventional forms of kinematic analysis so far used in early RA research. As intersegmental rotations occur at different angular velocities and directions, distinct regions of variability in segmental rotations occur during gait which conventional forms of data analysis are unable to measure

(Stergiou et al., 2001). At present, it is not known whether coordinated motion within the foot and lower limb is impacted in the presence of early RA. This is a significant omission; when the degrees of freedom of movement are reduced to a critical threshold, injury or disease may result (Lipitz and Goldberger., 1992).

Studying the variability of *inter-segmental* coupling may provide a critical measure of pathomechanics that has yet to be investigated in early RA. It is possible that in early RA, alterations in coordinative variability may play a key role in inducing mechanically based trauma to already pathologically compromised tissue. Given that segmental kinematics incorporate a spatial-temporal component (Riley and Turvey, 2002), using a parameter which incorporates the elements of space, time and motion would provide a novel approach when investigating pathomechanical function in early RA. Analysing coordinative variability may provide such a measure which has yet to be applied in 3D motion capture of early RA. Altered coordinative variability may represent an important injury mechanism that has yet to be elucidated, necessitating alternative methods of data analysis when moving forward with early RA research. If found to be present, alterations in coordinative variability may provide additional evidence supporting the view that pathomechanical foot function is an exacerbator of continued synovitis seen within the foot (Bowen et al., 2010).

2.3.14 Errors associated with 3D motion capture

Data collection using 3D motion capture is susceptible to error (Schwartz et al., 2004). Error represents the variance component of data not attributable to true variance (Bruton et al., 2000). This occurs primarily due to incorrect marker placement arising from ambiguities in the

segmental definitions of biomechanical models and investigator fallibility (McGinley et al., 2013). In developing protocols for future motion capture research in early RA, investigators must be confident that these are robust. Where these data are to be used for clinical decision making, this is of particular relevance. With this in mind, this section focuses on how sources of error may adversely affect 3D motion capture data.

2.3.15 Errors associated with lower limb kinematic data

The Conventional Lower Limb Model (alternatively known as the Plug-in Gait model) is the most widely used lower limb biomechanical model and has been previously validated for use in the three-dimensional motion analysis of the lower limb (Kadaba et al., 1990). A limitation of this model is the use of landmarks that may be only partially anatomical in nature when defining lower limb segments. This may result in errors in marker placement primarily affecting the repeatability of frontal and transverse plane data (Kadaba et al., 1990; Kadaba et al., 1991; Tsushima et al., 2003).

The definition of embedded axes at the hip and knee are highly dependent upon marker placement. Ramakrishnan and Kadaba (1991) reported that perturbation of the embedded axes within this model result in the flexion/extension axis of the hip and knee being displaced by up to 30 degrees, with sagittal plane data largely unaffected. Errors in knee abduction/adduction were found to reach 8-12° by midstance (60-80% of stance). During the early to mid-swing, (60-80% of swing) errors in abduction/adduction angle increase ($8\text{-}12^0$) with greater knee flexion ($40\text{-}60^0$). Hip abduction/adduction angle errors were relatively larger in the stance phase ($5\text{-}7^0$) with increasing flexion ($30\text{-}35^0$). In 40 able bodied participants, aged between 18 and 40 years, Kadaba et al., (1990) found that transverse plane rotations demonstrated the lowest magnitude of repeatability. Although this resulted in CMC values that ranged between

0.918 ± 0.087 (hip rotations) and 0.885 ± 0.053 (ankle rotations), marker placement did not appear to significantly affect within-session repeatability in these kinematic data.

Marker placement error may result in a decreasing hierarchy of repeatability. Tsushima et al., (2003) found that CMC values for transverse plane rotations were least repeatable, ranging from 0.812 ± 0.128 for knee rotations to 0.826 ± 0.120 for rotations at the hip, compared to sagittal plane rotations ranging from 0.993 ± 0.005 for hip flexion/extension to 0.975 ± 0.010 for ankle dorsiflexion/plantarflexion. Similarly, in a study by Meldrum et al., (2014) using the intraclass correlation (ICC) method, moderate to excellent repeatability of measures ranging from 0.63 to 0.84 were observed for sagittal plane rotations at the hip, knee and ankle. Frontal plane rotations at the knee were reported to be poor, ranging between 0.20 and 0.38 for varus and valgus movements respectively. In addition, internal and external rotations at the knee were also observed to suffer from high levels of error with ICC coefficients of 0.34 and 0.25 for external and internal rotations in the transverse plane.

2.3.16 Errors associated with lower limb kinetic data

Test-retest repeatability of kinetic measures have been reported to vary at different sites within the lower limb. Overall, the highest levels of repeatability appear to occur within the hip and for sagittal plane data in particular. Weiss et al., (2007) reported mean joint moments for the hip to range between 0.95, 0.93 and 0.81N/kg for extension, flexion and abduction at this joint. In terms of repeatability, Meldrum et al., (2014) reported ICC values for these parameters to be 0.81, 0.71 and 0.70 respectively. By comparison knee joint moments appear to demonstrate a lower magnitude of repeatability. Joint moments at the knee are lower than those seen at the hip with Weiss et al., (2007) observing joint moment values at this site to be 0.53, 0.45 and 0.51 N/kg for knee joint extension, flexion and valgus rotation. However, lower ICC values

were also observed by Meldrum and colleagues for the knee with respect to extension moments (ICC = 0.70) and flexion moments (ICC = 0.51). Ankle joint moments have been reported to be 1.49 N/kg for plantarflexion and 0.18 N/kg for dorsiflexion. In terms of sagittal plane repeatability at this site, Meldrum reported an ICC value of 0.67 (Meldrum et al., 2014).

2.3.17 Errors associated with foot kinematic data

Anatomical landmarks on the foot may be either difficult to palpate or even absent, leading to uncertainties in marker placement. Of the aforementioned multisegment foot models cited in section 2.3.3, only those published by Hyslop et al., (2010) and Leardini et al., (1999) describe midfoot kinematics. Of these, only the Leardini foot model was explicitly developed to meet international Society of Biomechanics (ISB) guidelines on the measurement and reporting of segmental kinematics (Wu et al. 2001).

But repeatability data for this model are limited. A study of two healthy participants (aged 27 years) by Deschamps and colleagues reported on the inter-trial and inter-rater repeatability of the Leardini Foot Model. This group observed that the greatest inter-session variability in mean angular rotations were seen in sagittal plane rotations at the Calcaneus-Midfoot (7.8°), Shank-Calcaneus (7.4°) and Calcaneus-Metatarsus (7.1°) segments. When inter-trial and inter-investigator data were combined and expressed as a ratio (r), variability at these sites remained highest with differences in joint angles being reported as 10.4°, 8.7° and 7.9° respectively. Inter-session variability was reported to be least at the Shank-Foot and Calcaneus-Metatarsus (1.9°) segments.

Deviations in marker placement at the sustentaculum tali and peroneal tubercle result in large excursions in the orientation of calcaneal reference frame and hence relevant joint angles (Carravagi et al., 2011). This is subject to a learning effect. A study of 8 participants (mean age 48 ± 15.4 years) using a repeated measures design by Deschamps et al., (2012) found that within-day and between day repeatability of data collected between senior and junior clinicians varied. Using a z-score based analysis of mean range of motion data, 83% of absolute measurements by senior investigators were found to have a similar z-score, decreasing to 74% where data were collected by less experienced staff (Deschamps et al., 2012). A follow up study published in the same year by this group found that in six participants (age range 22 – 54 years), CMC values for kinematic data ranged between 0.782 and 0.987, reducing to 0.693 and 0.991 for an inexperienced investigators. Between-day CMC values were similarly affected (Deschamps et al., 2012). Despite the propensity for error, this group found that the overall inter-trial variability for all segmental rotations in the LFM was less than 3° (Deschamps et al., 2012).

2.3.18 Future directions

Three-dimensional motion capture has in part elucidated how alterations in segmental kinematics manifest in early RA. In extending the clinical utility of previous research, additional investigation is required to ensure that protocols for 3D m3otion capture are robust enough to reduce error to within levels acceptable for clinical decision making.

2.4 Surrogate measures of pathomechanical function in early RA

Whilst it has been argued that some form of musculoskeletal assessment should be carried out on patients with early RA (Woodburn et al., 2010), the nature of this assessment in current guidelines published by the Primary Care Rheumatology Society (PCR) and the Arthritis and Musculoskeletal Alliance (ARMA) is unclear (ARMA, 2004; PCR, 2011). Currently, 3D motion capture is not widely for the assessment of physical impairment in these patients. The following sections focus on measures of disease activity and disease impact which are currently used as surrogate measures of physical impairment.

2.4.1 Disease impact

In the absence of specific guidelines on the musculoskeletal assessment of the foot and lower limb in early RA, rheumatology function tests (RFT) are used to assess the presence of physical impairment. Whilst these tests are among the most reproducible metrics used in clinical rheumatology, they are not direct measures of foot and lower limb kinetics and kinematics. In translating the results of laboratory based 3D motion capture research on early RA into clinical practice, it must be acknowledged that the utility of this technique may preclude its use in clinical practice (Schurr et al., 2017). Whether RFTs have an explanatory capacity of segmental kinematics to allow their use as alternative surrogate measures of lower limb physical impairment in early disease has yet to be determined. The following sections describe those tests of physical function currently validated for use in laboratory based research and clinical practice.

2.4.2 Rheumatology physical function tests

The conceptual framework of physical disability is modelled as the explicit interaction between four sequential stages: pathology → impairment → functional limitation → physical disability. Within this framework functional limitations are defined as restrictions in basic physical actions normally viewed as involving the whole person (Escalante et al., 2002). As the rate of functional decline in patients with early RA increases sharply following initial diagnosis a decline in the capacity to perform specific Rheumatology Function Tests (RFT) is used to provide quantifiable and reproducible information concerning a patients currents functional status and future prognosis (Pincus and Callahan, 1992).

Measurements of grip strength, timed walking and button time have been shown to be reliable objective assessments of functional status in patients with RA (Sokka et al., 2003). These measures of functional status demonstrate generally higher levels of significance than radiographic scores or laboratory tests when predicting long term outcomes such as disability status and predict premature mortality (Pincus and Sokka, 2003). Furthermore, these tests are among the most reproducible measures used in clinical rheumatology. Because global measures are significantly correlated to patient status, they do not change sufficiently over time to be useful for monitoring patients quantitatively (Pincus and Callahan, 1992). Therefore, functional status is recognised as important in assessment and monitoring patients with RA. When assessing the impact of RA on physical function, performance based functional measures are seen as well suited to the quantification of functional impairment in RA as they measure physical actions performed by the intact person and are not subject to socio-cultural influences (Pincus, 2005).

2.4.3 Grip strength

Muscle weakness in RA is considered to be indicative of the presence of generalized disuse atrophy (Häkkinen et al., 2006). Whilst being primarily a test of upper body physical function, grip strength in early RA is therefore viewed as a determinant of global functional capacity. Grip strength has been shown to discriminate between disease activity states in early RA, based upon the presence of decreasing physical performance (Sheehy et al., 2013). A decline in muscle strength has previously been reported to be associated with disease activity and disability (De Santanna et al., 2014). Decreased muscle strength in RA has also been associated with worse physical performance and difficulties in carrying out activities of daily living. Significant and progressive loss of grip strength has been shown to be significantly correlated to global HAQ function. Häkkinen et al., (2006) found that decreasing grip strength acts as an explanatory factor of self-reported physical function in the HAQ sub-dimensions of 'eating', 'reach', 'grip' and common activities of daily living, including 'walking'.

2.4.4 Timed button test

In the context of RA, the timed button test involves asking the subject to button and unbutton a shirt or button board as quickly as possible, with results expressed as the number of buttons fastened/unfastened per minute (Pincus and Sokka, 2003). A baseline value for a timed button test of less than 40 seconds predicts a survival rate of 90% at 15 years compared to 50% at 5 years and 30% at 15 years where baseline levels were greater than 120 seconds. This test quantifies both large and small upper extremity joints (Escalante et al., 2004).

2.4.5 Timed walking

When considering those RFT specifically validated to assess lower limb functional impairment, only timed walking is recommended for use in RA. A modified walking time of less than 10 seconds along a 30 metre walkway has been shown to predict a 90% survival rate at 5 years and 70% at 25 years compared with a survival rate of 50% at 5 years and 30% at 15 years where the baseline values were greater than 30 seconds (Fransen and Edmonds, 1999). In addition, Pincus and Sokka (2003) note that both inter-rater and intra-rater reliability for this test are excellent.

2.4.6 Timed up and go

More recently, timed up and go (TUG) has emerged as a test to evaluate functional capacity across a series of specific manoeuvres. TUG measures, in seconds, the time taken by a subject to stand up from a standard chair, walk a distance of 3 metres at self-selected walking speed, turn and then walk back to the same chair and sit down. Initially developed for the assessment of elderly individuals at risk of falls, TUG is now a widely used simple measure of basic function. This test has been shown to be predictive of falls within elderly community dwelling adults (Hayes and Johnson, 2003). More recently its use has been extended to the assessment of specific pathologies including multiple sclerosis (Nilsagard et al., 2007) and osteoarthritis (Murphy et al., 2011). TUG has yet to be studied in the context of early RA. However, in a study of the applicability and reliability of balance tests in patients with peripheral arthritis, Noren and colleagues (2001) concluded that TUG may be applicable to those patients with moderate to severe disability including RA (Noren et al., 2001). Both a high inter-rater and intra-rater reliability have been reported for TUG. In addition, criterion validity has been

reported as moderate compared to other functional tests such as gait speed and Berg balance test (Hayes et al., 2000).

2.4.7 Future directions

It may be argued that given their inter-professional use within both the clinical and research settings, there is a question as to whether RFT can be used clinically as proxy measures of lower limb altered lower limb kinematics? This is a question that has yet to be answered. Given the need for assessment tools that are quickly and easily prescribed (Pincus, 1992), demonstrating such explanatory relationships with early RA kinematics may identify clinically cost effective and validated alternatives to the use of 3D motion capture in the musculoskeletal assessment of early disease

2.4.8 Disease Activity

The burdens of time mean that within the clinical setting functional capacity is more likely to be inferred by measuring disease activity, than through the prescription of rheumatology function tests (Aletaha et al., 2009). The surrogate use of disease activity is based upon the premise that once the transition from early to established disease has taken place, the long-term accumulation of radiographic damage and thus physical impairment may be considered a reflection of disease history. It is unclear whether disease activity measured using composite indices or single measures has an explanatory role in the presence of altered kinematics in early disease. It is also unclear whether disease impact measured using self-reported questionnaires has an explanatory role. The following sections describe how disease activity is currently assessed.

2.4.9 Composite indices used in early RA

There is no single *gold standard* quantitative measure to assess and monitor the clinical status of patients presenting with early RA (Smolen et al., 2005). Instead, disease activity may be assessed using a variety of measures including laboratory tests, radiographic scores, formal joint counts, self-reported questionnaires and measures of physical function. For this reason, several composite indices have been validated for use in RA that provide a single estimate of disease activity from multiple data: DAS, DAS28, Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI). A hallmark of these indices is the algebraic calculation of disease activity using data from swollen and tender joint counts combined with acute phase reactants. In calculating disease activity these indices differ in the number of tender and swollen joints that are counted. Apart from CDAI, all incorporate acute phase reactants.

2.4.10 Reproducibility and concordance of disease activity measures

Little separates these indices in terms of their reproducibility and concordance. In what is considered a landmark study of the DAS, Van der Heijde et al., (1990) reported test-retest of this measure to have a correlation coefficient of 0.89. Similarly, the reproducibility of a later iteration of the DAS, the DAS28, has been reported to be excellent in two studies by Virijhoef et al., (2003) and Walsh et al., (2008) with ICC values of 0.82 and 0.89 being reported respectively. When direct comparisons were made between the DAS28, SDAI and CDAI, ICC values have again been shown to be excellent at 0.88, 0.82 and 0.89 respectively (Virijhoef et al., 2003).

Concordance between indices has also been reported. In a study of 223 early RA participants, Ranganath et al., (2007) reported concordance between the DAS and DAS28 to be moderate to good at 77% in terms of DAS44 defined treatment response. Similarly, Van Gestel et al., (1998) reported a treatment concordance of 86.7% in a study of 105 early RA patients. Concordance between the DAS28 and SDAI have also been reported to range from 0.82 to 0.89. When the DAS28 was compared against the CDAI, concordance was again very good, ranging from 0.89 to 0.93 (Ranganath et al., 2007).

2.4.11 Metrological ranking of disease activity measures

Ranking these measures according to their metrological properties is also difficult. What separates these measures is their ability to discriminate between disease activity cut-off points, specifically in the presence of remission in early RA. This is a key factor determining the construct validity of composite indices used in RA. When comparing the ability of the DAS28 and DAS44 to discriminate between patients in remission according to ARA criteria, area under the curve (AUC) values have been found to be similar: DAS28 AUC = 0.93 [0.92 – 0.94] versus DAS44 = 0.96 [0.95 – 0.97] (Soubrier at al., 2006). Construct validity appears to be dependent upon disease duration. Aletaha and colleagues reported that when correlations between disease activity and physical function were studied in 998 patients in the first 8 years of disease, correlations between HAQ score and the DAS28, SDAI and CDAI showed similar-to-fair correlations ranging from r = 0.45 – 0.47 (Aletaha et al., 2005). By contrast, the presence of early disease, correlations were much weaker, with r values ranging between 0.26 – 0.31.

In reality, it is difficult to ascertain whether one disease activity measure is superior; all appear to be valid tools. Determining their ranking according to metrological properties is difficult except for where remission is concerned. Despite the DAS28 being accepted, its implementation in daily practice remains a challenge; it has been considered less reproducible owing the larger number of joints evaluated, including those within the feet. This does not however appear to have been investigated or demonstrated. Consequently, of the aforementioned indices the DAS28 is officially recommended by EULAR and is considered most widely used measure of disease activity in clinical practice.

2.4.12 DAS28

Originally developed and validated by Van der Heijde and colleagues as the DAS (van der Heijde et al., 1992), this composite measure of disease activity was subsequently modified by Prevoo et al., (1995). Derived from counts of 28 tender and swollen joints, the erythrocyte sedimentation rate (ESR) and global health measured by a visual analogue scale (Hameed et al., 2008). The DAS28 was specifically designed for use in the assessment of patients with early RA and has become the most widely used measure of disease activity in RA (Symmons, 2010) recommended within NICE and British Society of Rheumatology (BSR) guidelines for use in the assessment patients with RA (Luqmani et al., 2006). The DAS28 provides a continuous numerical range from 0 to 10 in which a score of >5.1 implies high disease activity, a score of <3.2 implies low disease activity, whilst a score of <2.6 indicates remission as defined by the American Rheumatism Association (Prevoo et al., 1995).

In the Combinatietherapie Bij Reumatoide Artritis (COBRA) trial cohort, single values of the DAS28 were shown to be significantly longitudinally associated with radiographic progression (Welsing et al., 2006), whilst Koevets et al., (2013) concluded that the main clinically relevant predictor for disability, showing the largest size effect was the DAS28 (β=0.250 95% CI 0.220 to 0.280). Importantly, fluctuations in DAS28 disease activity appear to have an independent effect on radiographic progression with the strength of the associations between fluctuations and radiologic progression being dependent upon RF status and/or baseline disease activity. As a result, although high peaks in disease activity result in additional damage, periods of low disease activity in an otherwise fluctuating disease course are not protective (Welsing et al., 2004).

2.4.13 Limitations of the DAS28

As a measure of disease activity, the DAS28 primarily focuses on evaluating the impact of RA within the upper body; it does not evaluate the impact of RA below the level of the knee. It is for this reason that the most frequent criticism of the DAS28 is that it does not include an evaluation of the joints of the ankles and feet, commonly involved in early RA. This may profoundly limit the use of DAS28 driven measures of disease activity in assessing physical impairment in early RA. In a study of 155 patients treated with DMARDs combined with high dose oral prednisolone, Landewe and colleagues noted that in paired observations between the DAS28 and DAS, omitting the joints of the foot resulted in discordant observations of remission in 96% of patients where only the 28 joint count is used (Landewe et al., 2006). Because composite indices such as the DAS28 omit the joints of the foot, it is plausible that even within remission status, long term morbidity may still occur. The observation that both the CRP and ESR are within normal range in 45% of patients may further exacerbate the

potential for the underestimation of active foot pathology in early RA (Sokka and Pincus, 2009). This view was endorsed by Wechalekar et al., (2012) who found that in 123 DMARD treated patients studied within the first six months of disease activity, the percentage of those exhibiting foot synovitis reached 43% regardless of DAS28 defined disease activity.

Investigating the disassociation between composite measures of disease activity in the presence of synovitis, Dale and colleagues used musculoskeletal ultrasound (MSUS) of the metatarsophalangeal joints (Dale et al., 2014). Investigating 111 patients with disease duration of up to five months treated with step-up conventional and biological therapies, this group found that in the presence of moderate DAS28 defined disease activity, power Doppler signal was identified in ≥ 2 joints in 25% of patients. Furthermore, remission was not found to be protective of disease activity within these joint sites with power Doppler signal detected in 24% of patients.

A failure to detect active synovitis within the foot means that it is unclear whether the DAS28 has an explanatory role when identifying and monitoring altered foot and lower limb biomechanical function in early disease. Investigating this aspect is an area for further investigation that is required if the DAS28 is to be confirmed as a surrogate indicator of biomechanical pathology.

2.4.14 Health Assessment Questionnaire

Infrequently, measures of disease activity may also be supplemented with data from self-reported questionnaires, namely the HAQ. When defining the nature of lower limb functional

impairment, it may be conceptualised as the interaction between global health, personal and environmental factors. To this end the World Health Organisation (WHO) recommend the use of the International Classification of Functioning (ICF) to provide a framework within which physical impairment and disability may be described and organised (WHO, 2001). It is within this conceptualisation of 'function' using a biopsychosocial model that the Comprehensive ICF Core Sets for RA have been derived.

The HAQ is used to evaluate disease impact benchmarked against ICF core sets in RA. Designed and validated by Fries et al., (1982) as an adjunct to clinical examination, the HAQ provides a quantitative measure of the impact of disease activity on physical function with category scores ranging from 0 – 1 (mild impairment); 1 – 2 (moderate to severe); 2 -3 (severe to very severe). Recommended by NICE, the HAQ is distinct from measures such as laboratory and radiographic examinations. The HAQ has been shown to be sensitive to current disease activity and cumulative damage (Pincus and Sokka, 2003). In addition, the HAQ is a good predictor of global health in patients with RA (Pincus and Sokka, 2003). Several modifications of the HAQ have been reported with the Modified HAQ (MHAQ) providing a simplified scoring system allowing clinicians to visualize activities of daily living (ADL) scores as well as Visual Analogue Scales (VAS) for pain and global status in an abridged format (Prevoo et al., 1995; Ringold and Singer, 2008). A further modification of the MHAQ incorporates six additional ADLs to the eight already included in the MHAQ and is referred to as the Multi-dimensional HAQ (MDHAQ). In addition, the Clinical HAQ (CLINHAQ) incorporates the domains of anxiety and depression as additional items (Prevoo et al., 1995; Ringold and Singer, 2008).

2.4.15 Limitations of the HAQ

In evaluating the impact of early RA on lower limb physical impairment it is possible that there are limitations to using the HAQ. Because physical Function and Disability as defined by the ICF is broad conceptually, an instrument such as the HAQ which exclusively covers the components of activity and participation must be selective in its incorporation of which core sets to use. From a pragmatic perspective the omission of these data may simply reflect those ICF Core Sets which cannot be measured using self-administered questionnaires. Their omission may however also reflect wider attitudes concerning how physical impairment and disability in RA is interpreted and measured within rheumatology communities. As a result, the manner in which ICF Core Sets are incorporated into measures such as the HAQ therefore define the parameters within which physical function and disability are assessed in RA.

The manner in which ICF categories are selected may therefore introduce conceptual limitations in which lower limb function is assessed. Not only do the ICF Core sets provide guidance on what to measure; they also leave open to interpretation which measures to use. Of the twenty-five ICF categories appertaining to the component of "Body Functions" included in the Comprehensive ICF Core Set for RA, only "Sensation of Pain" is assessed by the HAQ. Related categories of lower limb physical function in RA not assessed by the HAQ are: "Pain in Lower Limb", "Gait Pattern Functions", "Mobility of Joint Functions", "Stability of Joint Functions" and "Mobility of Joints (Generalised)". Within the eighteen ICF categories of the component "Body Structures" none are assessed by HAQ that are specific to the lower limb. Importantly, this fails to consider "Structure of Lower Extremity", "Hip joint", "Knee joint" and "Structure of ankle and foot". Of the 32 categories within the component of "Activities and Participation", only "Walking" specifically assesses lower limb function. Whilst this

category is included within the HAQ, a greater emphasis is placed upon the specific assessment of upper limb impairment and disability or the global effects of upper body disease upon activities of daily living. Lastly, of the categories within the component "Environmental Factors" none are included within the HAQ that address the environmental contexts within which lower limb physical impairment or disability in RA take place.

2.4.16 Leeds foot impact scale

Within the conceptual framework of the ICF only the Leeds Foot Impact Scale (LFIS) has been developed as a patient reported outcome measure for use in assessing the impact of RA on the foot (Van der Leeden et al., 2008). In addition, the LFIS assesses constructs that are closely aligned to those of the domains of the ICF. The LFIS is both an evaluative and discriminative patient reported outcome measure that places a strong emphasis on the qualitative aspects of pain, stiffness and biopsychosocial experiences arising from the impact of RA on the foot (Walmsley et al., 2010). This measure consists of a self-completed questionnaire comprising of two subscales: impairment/footwear and activity limitation/participation restriction (van der Leeden et al., 2008a). The former contains 21 items related to foot pain, joint stiffness and footwear-related impairments. The latter contains 30 items relating to activity limitation and participation restriction. In addition, a visual analogue scale (VAS, 0 – 100mm) is used to record both global pain and joint pain in subjects.

2.4.17 Limitations of the Leeds Foot Impact Scale

The LFIS exhibits demonstrable measurement properties relating to reliability, construct validity and responsiveness (Helliwell et al., 2005). It has subsequently been used in a number

of cross-sectional, intervention and audit studies (Turner et al., 2006; Turner et al., 2008; Rome et al., 2011; Rome et al., 2013; Silvester and Williams, 2010; Muradin et al., 2016; Williams et al., 2016; Morpeth et al., 2016; Zou et al., 2017). Whilst developed to provide a wide applicability of evaluation of disease specific impact in RA populations, it was not designed specifically for sole use in early RA participants (Helliwell et al., 2005). Whether this affects the sensitivity and specificity of the LFIS when used in early RA participants has yet to be ascertained. Muradin and colleagues have recently cast doubt over the utility of the LFIS. When applied to patients not presenting with those characteristics not seen within the samples used in the original development of the LFIS. In participants with established disease presenting with advanced forefoot and rearfoot pathology, the LFIS was found to demonstrate moderate internal responsiveness when compared to the Foot Function Index (FFI). The sensitivity of 75%, specificity of 57%of the LFIS were also found to be affected compared to that of the FFI. The LFIS demonstrated below acceptable discriminative properties compared to the FFI**.** (Muradin and van der Heide, 2016). In addition, some doubts have been raised over the utility of the tool with respect to patient cognition of individual questions within each dimension (Carter et al., 2016).

In developing the LFIS, Helliwell and colleagues placed specific emphasis upon testing the unidimensionality of the tool as a disease specific measure applicable to all patients presenting with RA. This has resulted in dimensions of impairment and function that reflect perceptions of the disease based upon interviews from thirty patients presenting with both early and established disease in the absence of structural pathology (Helliwell et al., 2005). Whilst these may mirror those ICF classification criteria for the domains of impairment and function, specific consideration to the pathomehanical features underlying these dimensions were not given.

The relationship between the dimensions of 'impairment' and 'function' with altered foot kinematics in early RA is uncertain. As an alternative to 3D motion capture, whether the LFIS may act as a proxy of altered foot kinematics in early RA remains to be established. Caution should therefore be exercised when applying this tool to a specific sub-section of patients such as those presenting with early RA. Muradin and colleagues have recently cast doubts over the utility of the LFIS has been raised when applied to patients not presenting with those characteristics not seen within the samples used in the original development of the LFIS. In participants with established disease presenting with advanced forefoot and rearfoot pathology, the LFIS was found to demonstrate moderate internal responsiveness when compared to the FFI. The sensitivity of 75%, specificity of 57% of the LFIS were also found to be affected compared to that of the FFI. The LFIS demonstrated below acceptable discriminative properties compared to the foot function index (FFI**).** (Muradin and van der Heide, 2016).

2.4.18 Future directions

In the absence of specific guidelines on the musculoskeletal assessment of the foot and lower limb in early RA, composite measures of disease activity and self-reported assessment of disease impact have played a surrogate role in the clinical assessment of early RA. The question as to whether such measures relate specifically to alterations in lower limb kinetics and kinematics in early disease has yet to be answered. As these are parameters that underpin the onset of long term pathomechanical dysfunction, it may be argued that there is a clinical need for investigating their use in the assessment of early RA. Given the need for tests of physical impairment that are of low cost and easy administration, there may be a specific role in the assessment of musculoskeletal impairment in early RA that these tests may fulfil which current measures are unable to provide.

2.5 Justification for this PhD thesis

Three-dimensional motion capture has in part elucidated the presentation pathomechanics in early RA. To translate these laboratory based findings into clinical practice, more comprehensive data are required in order to optimise the recognition and targeted management of early musculoskeletal pathology in RA by clinicians:

1. In early RA, the kinematics of the foot and lower limb have yet to be investigated simultaneously using 3D motion capture. Clinicians cannot be completely certain as to where significant alterations in segmental kinematics of the hip, knee, ankle and foot are located within the first two years of disease.

2. Likewise, the magnitude and location of significant alterations in lower limb kinetics is also unclear.

3. The timing and duration of altered segmental kinetics and kinematics in early RA is unknown; between-group differences in the mode of variance of these parameters have yet to be elucidated.

4. Whether early RA affects the inter-segmental coupling of movement between the main functional units of the foot is unknown.

5. Whether early RA affects the inter-segmental coupling of movement between the foot and lower limb has is also unknown.

6. In the absence of clear guidelines and validated tools for the clinical assessment of musculoskeletal pathology in early RA, it is unclear whether rheumatology function tests, indices of disease activity and measures of disease impact can be used by clinicians as surrogate indicators of 3D laboratory based measures of biomechanical function.

2.6 Research Aims

In moving forward, the overarching aims of this research will be:

4. To establish reliable protocols for the 3D biomechanical evaluation of the foot and lower limb in subjects with early adult RA.

5. To quantify and characterise the baseline 3D biomechanical function of the foot and lower limb in adult patients with early RA determining if these characteristics differ from aged-matched healthy adults.

6. To analyse the relationship between foot and lower limb 3D biomechanical function and disease impact.

2.7 Research Questions

The specific research questions asked within this thesis are:

Chapter 5

1. When people with early RA are compared to age and gender-matched healthy adults, are there significant between-group differences in the kinematics of the foot and lower limb during gait?

2. When people with early RA are compared to age and gender-matched healthy adults, are there significant between-group differences in the kinetics of the foot and lower limb during gait?

Chapter 6

3. When people with early RA are compared to age and gender-matched healthy adults, are there significant between-group differences in kinematic coupling within the foot and lower limb?

Chapter 7

4. Is there an association between the biomechanical function of the foot and lower limb in early RA with measures of rheumatology physical function?

5. Is there an association between the biomechanical function of the foot and lower limb in early RA with measures of disease impact?

6. Is there an association between the biomechanical function of the foot and lower limb in early RA with measures of disease activity?

Chapter 3: Methodology

To achieve the aims of this PhD thesis, protocols were developed for the use of 3D motion capture in the analysis of spatial-temporal parameters, joint kinetics and joint kinematics in participants with early RA and age and gender matched controls. Protocols for the use of rheumatology physical function tests and self-reported measures of disease impact were also developed. This chapter describes these protocols, the overall research design of the thesis and the statistical techniques used for data analysis.

3.1 Research design

A prospective cross-sectional study design was used to compare the kinetics and kinematics of the foot and lower limb in participants with early RA to an age and gender matched control group. This research was conducted over three studies between January 2013 and December 2016. Study 1 (phase 1) investigated the repeatability of 3D motion capture and foot posture assessment protocols at the beginning of the research. Study 1 (phase 2) investigated the repeatability of these protocols at the end of the research. Study 2 (phases 1, phase 2 and phase 3) investigated between-group differences in foot and lower limb spatial-temporal, kinetic and kinematic data. Study 3 (phase 1 and 2) investigated explanatory variables of altered foot kinematics in early RA. Figure 3.1 summarises the research design.

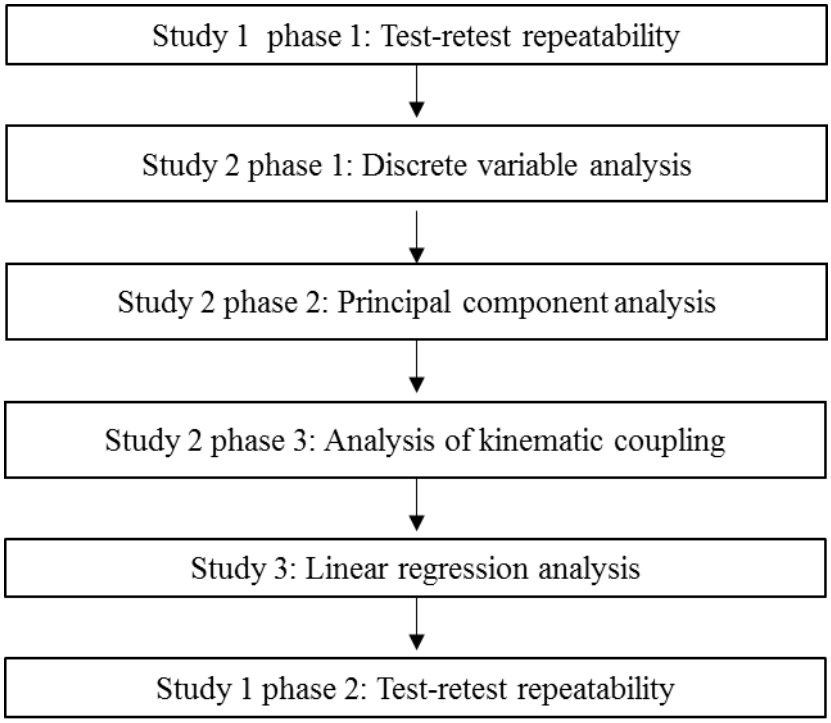

Figure 3.1: Summary of research design

3.2 Ethical approval

Ethical approval for this research was given by the National Research Ethics Service (NRES) Committee London – Bloomsbury: REC reference: 13/LO/0093 (Appendix 1) and the University of East London Research Ethics Committee (Appendix II).

3.3 Recruitment sites

The University of East London is located within a socioeconomically heterogeneous area of London in which high levels of deprivation and adverse healthcare outcomes have been reported (Department for Communities and Local Government, 2015). Invitations to recruit early RA participants from this area were sent to three recruitment sites: Homerton University Hospital, Whipps Cross University Hospital and Mile End Hospital. As part of Bart's Health

the combined catchment area of these sites encompasses four local authorities within East London area: Tower Hamlets, Newham, Hackney and Waltham Forest. Combined these local authorities represent 41.5% of the total population of East London (Office for National Statistics, 2011). Following initial consultations with these recruitment sites, Homerton University Hospital and Whipps Cross University Hospital agreed to participate as recruitment sites for this study.

3.4 Participant Recruitment

Two groups of participants were recruited. The first group consisted of adults diagnosed with early RA. These participants were identified by their rheumatology care teams during consecutive rheumatology out-patient appointments according to the inclusion/exclusion criteria of the research (Chapter 3, section 3.6). The second group consisted of a control group of healthy non-RA participants recruited from a convenience sample of volunteers from local community groups within the Newham, Tower Hamlets, City and Hackney and Waltham Forest areas.

3.5 Informed Consent

All prospective participants were given an information leaflet outlining, in layman's terms, the aims and methodology of this research (Appendix III). The aims and methodology of this research were also explained verbally by the Chief Investigator to all participants To avoid coercion or undue pressure to participate, all early RA and control group participants were given the option of 'opting in' to this research project. All participants were given the option

of leaving at any stage without prior explanation or disadvantage to themselves. Prior to data collection each participant gave written informed consent (Appendix IV).

3.6 Sample Size

Chapter 2 (section 2.3.6) highlighted the limited availability of published data on significant between-group differences in foot and lower limb kinetics and kinematics in early RA. To estimate the sample size required for this study, data from the first 10 early RA participants were therefore analyzed against 10 age and gender matched controls. Anthropometric data on these participants are presented in table 3.1. Data on the aforementioned parameters were used to estimate sample size using the formula $n \geq \frac{2\kappa\sigma^2}{\Delta^2}$ where n represents the population size, σ represents the variance in the groups being compared, κ represents the multiplying factor for the sample size formula at a 5% two-sided significance level at 80% power and Δ represents the minimum difference that this research was required to detect (Portney and Watkins, 2009). Table 3.4 presents the results of these analyses.

Table 3.1: Mean ± SD of anthropometric data for the first 10 early RA and 10 control group participants

Parameter	*Control Group (n = 10)*	*Early RA Group (n = 10)*
Male: female gender	6:4	7:5
Age (years)	43.9 ± 7.58	45.5 ± 9.75
Height (cm)	165.20 ± 9.89	173.14 ± 8.68
Weight (kg)	74. 00 ± 12.95	77.57 ± 10.54

Table 3.2: Sample size calculations based upon the Mean ± SD of foot and lower limb kinematic data from the first 10 early RA participants

Parameter	*Plane*	*Difference (°)*	*Mean SD*	*Required Sample Size*
Hip	Sagittal	0.62	5.55	773
Knee	Sagittal	4.56	4.22	61
Ankle	Sagittal	6.31	7.54	140
Shank-Calcaneus	Frontal	0.74	2.94	124
	Transverse	0.53	2.82	106
First MPJ	Sagittal	20.45	32.07	784

The numbers of participants needed to reach the required sample size calculations were beyond the magnitude of the recruitment rates achieved for this study. The numbers of participants required for the present study ranged from 61 to 773. By contrast, data from 32 early RA participants were collected for this study. Of these participants, 18 agreed to provide 3D motion capture data. Power calculations using mean and standard deviations from the final recruited sample of early RA participants therefore demonstrated statistical power ranging from 90.7% (frontal plane motion of the shank-calcaneus) to 15.7% (sagittal plane motion of the hip). The generalizability of the results of this research to the wider UK early RA population may therefore be considered uncertain and the present study may be regarded as exploratory in nature (Polgar and Thomas, 1995).

3.7 Inclusion Criteria

Early RA participants: Participants presenting with RA, aged between 25 – 60 years and with an ability to walk unaided were recruited within two years of initial diagnosis.

Control group participants: Healthy, non-RA participants, aged between 25 – 60 years (prior to key age related changes to musculoskeletal health) with no history of systemic disease, trauma and orthopaedic surgery were invited to participate in this research. Control group participants were age and gender matched to early RA participants.

3.8 Exclusion criteria

Both early RA and control participants were excluded where there was a prior history of foot and lower limb surgery or any systemic condition other than RA that might affect foot posture or cause a disturbance in gait.

3.9 Protocols for investigating foot and lower limb musculoskeletal function in adults with early RA and controls

The following sections describe the protocols used for investigating foot and lower limb musculoskeletal function using 3D motion capture in early RA and control group participants.

3.9.1 Three-dimensional motion capture system

Spatial-temporal, kinetic and kinematic data were collected simultaneously using an on-line stereophotogrammetry system. The hardware used for 3D motion capture consisted of: (1) A ten camera VICON Nexus system used to track auto-reflective markers applied to the foot and lower limb (Vicon Motion systems Ltd, Oxford, UK); (2) Twenty-nine 14mm auto-reflective markers, each mounted on a polyethylene base (Vicon Motion systems Ltd, Oxford, UK); (3) Two six-component force plates (Bertec, Model 4060-10 MIE Ltd. UK, Bertec, Model 4060-15 MIE Ltd. UK).

Cameras were wall mounted in a combined orthogonal and non-orthogonal configuration and directed between 60° and 90° towards the centre of the laboratory. The size of the capture volume measured approximately 4 x 1.5 metres and was sited in the middle of a 10 metre walkway. This camera arrangement ensured that at least three cameras were able to detect each auto-reflective marker, thereby reducing the *dead space* that falls outside of the cameras field of view.

3.9.2 Force plates

Two force plates embedded in the floor of a 10 metre walkway to record ground reaction force GRF). Analogue data from these force plates was amplified and transferred to the Vicon data station. Ground reaction forces were sampled at 1500 Hz.

3.9.3 Camera sampling rate and sensitivity

To optimise the reconstruction of markers prior to the calibration of cameras, sensitivity was set at 1500Hz. Kinematic data was sampled at 100 Hz and recorded digitally on a personal

computer. Reflective objects within the laboratory which may have provided extraneous sources of reflection resulting in false marker interpretations were identified and removed in order to preserve the integrity of the calibration process. Cameras were then masked.

3.9.4 Static calibration

To ensure that the image co-ordinates for each camera view were converted into the three dimensional co-ordinates of each marker, cameras were calibrated prior to each motion capture session. This was undertaken by setting the volume origin of the laboratory by capturing and reconstructing three markers of known location attached to a rigid 'L frame' placed at the corner of one force plate. This established the origin and location of the laboratory-fixed global axes.

3.9.5 Dynamic calibration

A dynamic calibration was undertaken using a calibration wand mounted with two auto-reflective markers of known location in a 'T' configuration to determine the residual mean. The orientation of the wand was moved through the capture volume for a duration of 10,000 frames to determine the residual mean. The residual mean is an indication of the position of each marker in space against its true position. For example, a residual mean of 1.0mm indicates that each marker can be located within 1mm of its true position. The residual mean appropriate for the size of capture volume used for this study was set at <1mm, along with wand visibility of > 65%. A successful calibration was therefore defined where residuals from marker position and inter-distances standard deviation were less than 1mm and wand visibility exceeded 65%. The capture volume area calibrated was 1.5m high, 2m long (direction of gait) and 2m wide.

3.9.6 Force plate calibration

Prior to calibration both force plates were switched on at least 30 minutes before testing to allow the force transducer system to reach thermal stability. An auto zero function provided on the external amplifier of the force plates allowed for zeroing offset loads to full scale. Force plates were calibrated separately using known weights of 10kg placed within the centre of each force plate. Vertical GRF was recorded and a correction factor applied to align each force plate reading to the correct acceleration due to gravity calculated to be -98N.

3.9.7 Laboratory co-ordinate system

The laboratory reference frame from which all positions originated was calibrated using an XYZ Cardan sequence with a right-handed orientation according to ISB recommendations (Wu et al., 2001). In the present study, the z axis was orientated vertically, the y axis was orientated along the walkway such as it was positive in the direction of progression and the x axis was orientated perpendicular to the other two axes and positive in the medial direction at right foot contact.

3.9.8 Order of data collection

Anthropometric and biomechanical data were collected on participants attending 3D motion capture study visits. Data were collected in the following order:

(1) Anthropometric measurements

(2) Foot posture assessment

(3) 3D motion capture

(4) Rheumatology function tests

3.9.9 Anthropometric measurements

To facilitate the calculation of joint centres and joint trajectories in 3D motion capture, the following anthropometric measures were taken: height, knee width, ankle width, leg length and weight.

Height: Height was measured in centimetres by asking each participant to stand under a portable stadiometer (Seca Medical Scales and Measuring Systems UK). Height was defined as the maximum distance from the floor to the highest point of the head with the participant looking straight ahead. Participants were asked to stand straight with their back against the stadiometer with both feet together and plantigrade to the floor.

Joint widths: Joint widths were measured in centimetres using an anthropometer (Holtain Ltd). Each participant was asked to stand in neutral rotation and base of relaxed static stance. Both left and right knee and ankle joint widths were measured. Knee width was defined as the distance between the medial and lateral femoral epicondyles. Ankle width was defined as the distance between the medial and lateral malleoli (Vicon Motion Systems Ltd).

Weight: Weight was measured in kilograms by asking each participant to stand on a pair of weighing scales (Seca Medical Scales and Measuring Systems UK). Participants were asked to stand on the centre of scales, without support and with their weight distributed evenly on both feet.

Leg length: Leg length was measured in centimetres from a straight line between the anterior-superior iliac spine and the ipsilateral medial malleolus using the direct method tape measure technique described by Asim et al., (2013).

3.9.10 Foot posture assessment

Measurements of foot posture were conducted on each participant on the day of testing using the Foot Posture index (FPI-6) described by Redmond et al., (2006). The internal construct validity of this index was observed by Keenan et al., (2007) to be compatible its clinical application, whilst a high level of intra-rater reliability for this measure was reported by Cornwall et al., (2009). As a clinical assessment tool, it has also been observed to remain robust, even when administered by novice examiners (McLaughlin et al., 2016).

Each participant was asked to stand in neutral rotation and base of relaxed static stance. The FPI-6 is, for the most part, an observational tool by which static foot posture is examined in all three cardinal body planes using the following criterion: (1) talar head palpation; (2) curvature above and below the lateral malleoli; (3) Calcaneal inversion/eversion; (4) talo-navicular congruence; (5) medial arch height and (6) Forefoot abduction/adduction. A summative score based on a continuous Likert scale classifies foot posture as follows: normal = 0 to +5, pronated = +6 to +9, highly pronated = +10, supinated = -1 to -4 and highly supinated = -5 to -12.

3.9.11 Lower limb biomechanical models

To facilitate the application of reflective markers on the lower limbs, all subjects were barefoot and wore shorts. Twenty nine reflective markers (14 mm spheres) were placed directly on the skin of the lower limbs. Two 3D biomechanical models were applied to each participant. The first model was the Conventional Lower Limb model. This was applied to the pelvis and both lower limbs. A second, multisegment foot model (Leardini Foot Model) was applied to the dominant or most symptomatic lower limb.

Segmental motion of the Leardini foot and Conventional Lower limb models was calculated using the joint co-ordinate system and expressed as *output angles* for each of the X, Y and Z axes. Output angles for the following segmental rotations were used to evaluate motion in early RA and control group participants: (1) hip joint; (2) knee joint; (3) ankle joint; (4) shank relative to calcaneus; (5) calcaneus relative to midfoot (6) MLA and (7) first MPJ.

3.9.12 Conventional lower limb model

The Conventional Lower Limb Model (Figure 3.1) is the most widely used lower limb biomechanical model and has been previously validated for use in the 3D motion analysis of the lower limb (Kadaba et al., 1990). The application of the Conventional Lower Limb Model followed protocols for the definition of segments, axes and output angles described by Davis et al., (1991).

3.9.13 Leardini multisegment foot model

The Leardini foot model is a five segment foot model that was applied to each participant undergoing gait analysis. This multisegment foot model was first described by Leardini et al.,

(2007) and validated for use in adults by Caravaggi et al., (2011). The application of the Leardini Foot Model (Figure 3.2) followed protocols for the segmental definitions, axes and output angle described in Leardini et al., (2007).

Figure 3.2: Marker Placement for the Conventional Lower Limb Model

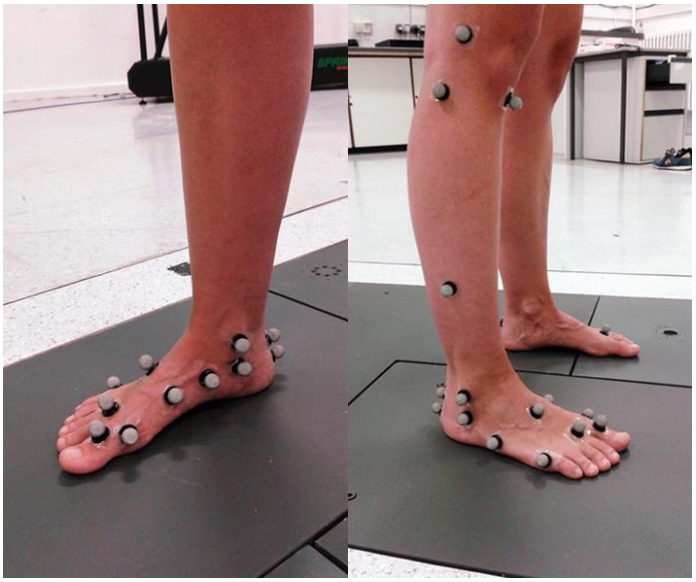

Figure 3.3: Marker Placement for the Leardini Foot Model

3.9.14 Data collection protocol

Static trial: To ensure that all auto-reflective markers were detected by the camera system, and to establish the position of joint centres for each gait model, a static trial of four seconds was recorded. Each static trial was recorded with the participant standing on the force plates within the capture volume. Participants were asked to stand facing in the direction of the Y-axis of the laboratory reference frame with their hands placed by their side and the lower limbs in neutral rotation.

Dynamic trial: Gait trials were recorded by asking each participant to walk barefoot along the walkway and through the capture volume at a comfortable self-selected walking speed. Participants were instructed to start walking on the command of "one, two, three, go". To allow participants sufficient time to accelerate to a self-selected walking speed a minimum of three steps were required on entering the capture volume. To allow sufficient deceleration a minimum of three step were required on exiting the capture volume.

To naturalise gait patterns and acclimatise participants to the conditions of the motion analysis laboratory, each participant was asked to carry out several practise gait trials. To acclimatise each participant to the conditions of the laboratory, practise trials were repeated until each participant could execute a complete gait cycle within the confines of the capture volume.

Perry (1992) described the phases of the gait cycle with respect to reciprocal foot contact with the ground. Within the capture volume, gait events were defined using the onset and termination of vertical force by the right foot on the force plates. Vertical ground reaction force above a threshold of 20N was used to identify initial contact of the dominant or affected lower limb. Contact with a second force plate above the 20N threshold determined initial contact and

toe-off events for the contralateral limb. Ipsilateral Initial contact and ipsilateral toe-off determined the stance and swing phases of the gait cycle.

Following acclimatisation to the laboratory conditions, up to 35 gait trials were recorded for each participant from which spatial-temporal, kinetic and kinematic data from six error free walking trials were analysed. A successful walking trial included the following: (1) one complete gait cycle per lower limb, consisting of one initial contact event, one midstance event and one toe-off event; (2) each participant was observed to walk through the capture volume in a straight line without targeting the force plates; (3) that the gait cycle events for each lower limb took take place within the confines of one force plate only and (4) all markers remained attached.

3.9.15 Protocols for evaluating rheumatology physical function and disease impact

Grip Strength: Grip strength was assessed by asking each participant to assume a sitting position with the elbow held at 90° with the forearm supported flat at horizontal. Grip strength was then assessed by compressing a dynamometer (Takai Instruments Corp, Japan) as hard as possible, three times with each hand with a one minute interval given between consecutive grip tests. The mean value was designated as the grip strength value.

Six Minute Walk Test: From a standing position, each subject was asked to walk across a thirty-metre walkway at comfortable self-selected walking speed and timed with a stopwatch. The distance in meters that each participant was able to walk in six minutes was then measured.

Timed Button Test: Participants were given a standard eight button shirt to wear and asked to button and unbutton the shirt as quickly as possible. The results were expressed as the number of buttons fastened/unfastened per minute. This was repeated three times. The mean value was designated as the timed button test speed.

Timed Up and Go: Participants were asked to stand up from a standard chair, walk a distance of three metres at self-selected walking speed, turn and then walk back to the same chair and sit down. The time taken for each participant to carry out this task was measured using a stopwatch. This was repeated three times. The mean value was designated as the timed up and go speed.

3.9.16 Measures of rheumatology disease impact

The number of painful joints that each early onset adult RA participant presents with were recorded using a participant reported painful joint count. To measure the impact of early onset adult RA on the foot, early onset adult RA participants were asked to complete the following additional outcome measures at this visit: (1) LFIS and (2) HAQ.

Leeds Foot Impact Scale and Visual Analogue Pain Scale: At the end of each testing session, early RA participants were given the LFIS to complete which was described in chapter 1. In addition, a visual analogue scale (VAS, 0 – 100mm) was be used to record pain on the day of testing.

Health Assessment Questionnaire: In order to evaluate key components of global disease activity, damage and functional ability each early RA participant was asked to complete the HAQ.

3.9.17 Data collection at NHS recruitment sites

The following data were retrieved from patient records held at individual NHS Trust sites:

Patient Demographics: name, age, gender and current RA specific drug therapy.

Measures of Current Disease Activity: Disease activity data were recorded using the DAS28, DAS-CRP, erythrocyte sedimentation rate (ESR), anti-cyclic citrulinated peptide (Anti-CCP), C-reactive protein (CRP) and rheumatoid factor (RF).

3.9.18 Data management

To minimise the dissemination of personal information and research data collected, only the Chief Investigator was responsible for data collection and data storage. The Chief Investigator did this in accordance with the Data Protection Act 1998.

3.9.19 Data processing

To avoid artificially increasing effect size and violating assumptions of independence only data from the dominant or affected limb were extracted for analyses (Menz, 2005). Vicon software was used to reconstruct marker trajectories. In total, two hundred and sixteen trials in which marker trajectories were visible throughout the entire gait cycle were used for analysis. Upon reconstruction, raw trajectories were filtered using the Woltring filter routine with the

recommended mean square error (MSE) value for filtering of gait data set at 20 (Vicon Motion Systems, Oxford).

Vicon Polygon® Plug-In-Gait software (Vicon Motion systems Ltd, Oxford, UK) was used to extract kinetic and kinematic data derived from the Conventional Lower Limb Model. C-Motion 3D® software (Visual 3D Inc, USA) was used to calculate and extract kinematic data derived from the Leardini Foot Model.

3.10 Statistical analysis

The following sections outline the statistical methods used to analyse data in this thesis. The descriptions of these methods are organised according to the study in which they were used.

3.10.1 Study 1: Evaluating test-retest repeatability

Chapter 2 (section 2.3.14) highlighted that 3D motion capture data is susceptible to measurement error. In statistical terms 'error' refers to all sources of variability in data that cannot be explained by the independent variable (Rankin and Stokes, 1998). Estimating the magnitude of error is therefore a fundamental determinant of what constitutes measurement repeatability and is attributable both to intrinsic and extrinsic sources.

3.10.2 Intrinsic variability

As part of the normal variation in human gait in able-bodied participants, it is normal to see variations in movement patterns and spatial-temporal parameters between gait cycles. This

natural variability is referred to as intra-subject (or intrinsic) variability. Such variability may be attributed to factors such as age, gender height and walking speed. Whilst experimental design may be used to control for these factors, their influence cannot be completely eliminated (McGinley et al., 2013).

The magnitude of intrinsic variability may vary depending upon joint site and plane of motion. Using the CMC method, Tsushima et al., (2003) studied intra-subject variability in six able-bodied participants (mean age 35.2 years ± 6.2), reporting sagittal plane rotations to demonstrate the lowest level of intrinsic variability, ranging from 0.997° ± 0.001 at the hip to 0.981° ± 0.005 at the ankle. Intrinsic variability may, however, increase when measured over time. Charlton et al.,(2004) reported a combined same day inter-trial variation in joint rotations of 2.90° ± 2.09 for the hip, knee and ankle motion, increasing to 3.09° ± 1.83, when measured between days.

By contrast, spatial-temporal data appear more stable. In a study of 5 participants (age range from 21-31 years, male/female ratio 2:3), analysing within-day and across-week variability in spatial-temporal parameters, McGinley et al., (2014) reported inter-session variability to be remained low with standard deviation values equal to or less than 0.05 m/s for walking speed, 2 steps/min for cadence and 0.03m for stride length.

Whilst natural variability is a consistent and modifiable feature of gait data, it should not be confused with measurement error. To estimate the error component of data it is important to

consider sources of variance which occur external to the participant which together constitute extrinsic variability.

3.10.3 Extrinsic variability

Three dimensional motion capture data are susceptible to extrinsic variability arising primarily from inaccurate marker placement and the movement of underlying soft tissue structures or artefact (McDermott et al., 2010). Because of this, variability in repeated measures taken between subjects and between-days has been shown to be the largest contributor to error in kinematic measures (Long et al., 2010). To mitigate against the effects of error in 3D motion capture data, repeatability studies assess how much measurements vary when they are repeated on the same participant under the same conditions. Repeated measures may be used to estimate between-rater variability, within-rater variability or inter-session variability. Distinguishing between these models is important when establishing protocols for repeatability analyses. How variability is analysed therefore depends upon the conceptual model of repeatability used as different models of repeatability may lead to different estimates of the variance component (Schwartz et al., 2004).

3.10.4 Analysis of extrinsic variability

In analysing the repeatability of 3D motion capture data, the approach of this thesis was to use two methods. In study 1, a conventional form of analysis was undertaken which examined the repeatability of spatial-temporal parameters, joint kinetics and joint kinematics using discrete variable analysis of data extracted from following events within the gait cycle: initial contact, midstance, toe-off and peak angular motions. The repeatability of these data was evaluated using the Standard Error of Measurement (SEM), Mean Difference and the Bland and Altman

limits of agreement (LOA). The level of agreement between repeated measures was evaluated using the Intraclass Correlation Coefficient (ICC). In contrast to conventional forms of repeatability analysis, a novel approach was used in study 2, based upon waveform symmetry analysis. This method was used to analyse the similarity in the shape, amplitude and excursion of 3D motion capture waveform data across the entire duration of gait. The following sections describe these methods.

3.10.5 Standard Error of Measurement

The standard deviation of measurement error reflects the reliability of a test measurement. For this reason it is incorporated into the SEM as a measure of absolute repeatability. The SEM is expressed in the units of measurement chosen for data collection. The SEM was calculated according to the method described by Portney and Watkins (2009):

$$\mathrm{SD} \times \sqrt{1 - \mathrm{ICC}}$$

3.10.6 Bland and Altman 95% Limits of Agreement

To assess agreement between test 1 and test 2 measurements, the Bland and Altman 95% LOA was used. This was calculated according to the method described by Bland and Altman (1986):

1. The mean of the test 1 and test 2 measurements was calculated along with the difference between the two means

2. The standard deviation of the two differences was calculated

3. The 95% limits of agreement was then calculated using the formula: $1.96 \times \frac{\Sigma(d2-d1)^2}{n}$

The 95% limits of agreement provides a range of error that may relate to clinical acceptability although this should be interpreted with respect to the range of measures in the raw data. Assuming errors are normally distributed it should be expected that 95% of the differences in test 1 and test 2 scores fall within 2 standard deviations above and below the difference between the mean of all measurements (more precisely ± 1.96).

3.10.7 Intraclass Correlation Coefficient

The intraclass correlation coefficient is a single index calculated using variance estimates obtained by partitioning measurement error into between and within subject variance. This is known as analysis of variance (ANOVA). The ICC reflects both the degree of consistency and agreement among measurements.

The level of agreement between repeated measures was evaluated using the ICC model (3, 1).

$$ICC = \frac{BMS - EMS}{BMS + (\kappa - 1)EMS}$$

Where BMS represents the between subject variance, EMS represents the residual variance and subscript kappa (κ) represents the number of raters.

The acceptance criteria for the ICC used in phase 1 followed guidelines recommended by Portney and Watkins, 2009). Therefore a correlation coefficient of <0.50 was defined as poor.

A correlation coefficient between 0.50 – 0.75 was classified as moderate whilst coefficients between 0.75 – 0.90 were accepted as good.

3.10.8 Waveform symmetry analysis

To assess the similarity of kinematic waveform data, a novel approach was used to examine the repeatability of all data points across the gait cycle. Waveform symmetry analysis was conducted using Matlab 2016a according to the method described by Crenshaw and Richards (2006). For each variable the following parameters were calculated: trend symmetry, range offset, and range amplitude for all three planes of motion. A fourth variable, phase offset, was calculated for sagittal plane parameters only. Trend symmetry is a unitless metric and was measured using eigenvector analysis using the following steps:

1. The mean value of each kinematic waveform was subtracted from each time-point in the data series:

$$\begin{Bmatrix} Xti \\ Yti \end{Bmatrix} = \begin{Bmatrix} Xi \\ Yi \end{Bmatrix} - \begin{Bmatrix} Xm \\ Ym \end{Bmatrix}$$

Each kinematic curve was represented by X and Y, respectively. Subscript *i* indicates the original data, *ti* indicates the translated elements after the data were demeaned, and the mean of each curve is indicated by subscript *m*.

2. These data were entered into a matrix containing each pair of points as a row.

3. Eigenvector analysis was then conducted using a singular value decomposition was applied to this matrix, multiplying it by its transpose:

$$(M = U\Sigma V^T)$$

Here, M represents the original *m* x *m matrix*, U represents an *m* x *m* orthogonal matrix , Σ represents an *m* x *n* diagonal matrix and V^T represents the original matrix transposed.

4. Each row of the resultant matrix was rotated by the angle measured between the eigenvector and the X-axis (Θ). This rotation caused the points to lie about the X-axis:

$$\begin{Bmatrix} X_{Ri} \\ Y_{Ri} \end{Bmatrix} = \begin{bmatrix} \cos\theta & \sin\theta \\ \sin\theta & \cos\theta \end{bmatrix} \begin{Bmatrix} Xti \\ Yti \end{Bmatrix}$$

Subscript *Ri* indicates the rotated elements and subscript *ti* indicates the translated elements of each data set.

5. The variability of data points was calculated along both the X and Y axes. X-axis variability was the variability along the eigenvector, whilst Y-axis variability was the variability about the eigenvector.

6. The trend symmetry value was computed by dividing the Y-axis variability (variability about eigenvector) by the X-axis variability (variability along the eigenvector) and was expressed as a percent.

7. This value was subtracted from one. A value of zero indicated perfect asymmetry. A value of one, indicated perfect symmetry. Values ≥ 0.95 were considered highly similar

between modes based upon a sagittal plane normative gait database (Crenshaw and Richards, 2006).

Range offset was measured as the mean difference, in degrees, between kinematic curves. A value of zero indicated that the mean value was the same for both waveforms. Positive values indicated the test 1 waveform to be greater in amplitude than that of the test 2 waveform.

Range amplitude was calculated as the ratio of the relative excursion (max value minus min value) between kinematic waveforms (test 1 versus test 2) and therefore unitless. A value of one indicated that the kinematic curves had the same excursion. Values larger than one indicated excursions were greater in the test 2 waveform.

The phase offset was calculated for the sagittal plane only as the other planes do not undergo large enough excursions. To calculate the phase offset one kinematic waveform was shifted by a 1% stance increment relative to the other. The trend symmetry number was then calculated. This shifting was repeated for every 1% of stance up to 20% stance in both forward and backward increments. The percentage of stance where the maximum trend symmetry value was identified was determined as the phase offset.

3.10.9 Test-retest repeatability of foot posture assessment

To investigate the repeatability of foot posture assessment, Rasch analysis was undertaken in study 1 to allow the analysis of categorical data from the FPI-6 using parametric statistics.

Rasch analysis is a probabilistic testing procedure that is used to assess outcome scales against a mathematical measurement model. This method was used in order to operationalize those

axioms thought to define foot posture, modelling the probability that foot posture assessment acted as a function of both the chief investigators operation of the FPI-6 and the response of individual criterion when applied. This was undertaken by calculating the probability of a correct response as the logistic function of the difference between the person and item parameter (Tennant and Conaghan, 2007). Fundamentally, Rasch analysis was therefore undertaken to characterize both the proficiency of the chief investigator in completing the FPI-6 and criterion difficulty as locations on a continuous latent variable.

Each criterion is viewed within Rasch analysis as a fundamental trade-off between the abilities, attitudes, or person traits of the clinician and the difficulty of measuring individual criterion (Tennant and Conaghan, 2007). Using a probabilistic form of Guttman scaling, response patterns achieved from a set of items in an outcome measure that are intended to be summed together are tested against what is expected by the model (Guttman, 1950). A Rasch model therefore describes the structure which data should exhibit in order to obtain measurements from that data, providing a criteria for successful measurement. In doing so, it provides an experimental benchmark, or model, against which data must fit (Andrich, 2004).

Rach models may be either dichotomous or polytomous. Tennant and Conaghan., (2007) advise the use of a polytomous model where categorical data are organised in ascending magnitude and where Likert-type scales are applied such as those used within the FPI-6. For these reasons, a polytomous mathematical derivation of the Rasch model first described by Andrich, (1978) was chosen. The algorithm for this model is described here in a simple logit-linear form: $\log(Pnij / Pni(j-1)) = Bn - Di - Fj$ (1) where $Pnij$ is the probability that participant

n encountering item *i* is observed in category *j* of a set of ordered response categories *j* = *s* + 1, *s* + *m*,. *Bn* is the ability of participant *n, Di* is the difficulty of item *I and Fj* is the Rasch-Andrich threshold located at the point of equal probability of categories *j*–1 and *j*.

To test the fit of data to the model used for this study, Rasch analysis used Chi-square based statistics to test the difference between observed and expected responses for criterion that demonstrate a difficulty level near the person's ability level:

New difficulty logit: This estimate is used to express item difficulty on a linear scale that extends from negative infinity to positive infinity. Under normal circumstances, item difficulties range from −3 logits to +3 logits.

Person standard error: This shows the precision of the Rasch estimate. The size of a standard error of an estimate is strongly influenced by the number of measurements used to make the estimate and should be no more than 3 standard errors difference.

Infit Mean Squares (MnSq): A mean-squares estimate near 1.0 indicates little distortion of the measurement system. The Infit MnSQ should normally be near 1.0. A MnSQ of above 1.0 may be considered high.

Rasch analysis was performed using WINSTEPS® software to transform ordinal data from the six component criterion scores of the FPI-6 into interval data prior to analysis using parametric statistics. Before entering data, item calibration was undertaken by scaling data (+1 to +5) in order to eliminate negative numerals. Once Rasch analysis was completed for both test-retest data on FPI-6 was performed, transformed summative scores of the FPI-6 were analysed using the ICC method described in section 3.9.6 of this chapter.

3.10.10 Study 2 - Comparative cross sectional study of adults with early RA compared against age and gender matched controls

Statistical analyses were performed using SPSS Version 22.0 and Microsoft Excel Version 2013. To assess for normality of distribution, data was assessed using the Shapiro-Wilk test. Between-group comparisons of spatial-temporal, kinetic and kinematic data were examined using independent t tests for normally distributed data and Mann-Whitney tests for non-normally distributed data. The level of significance used was 0.05 and all data reported as means ± SD.

3.10.11 Principal component analysis

In the presence of disease, 3D kinetic and kinematic waveforms may vary significantly in their shape and magnitude from those of healthy controls. To determine where dominant modes of variance occur between waveforms, principal component analysis (PCA) was carried out using SPSS Version 22.0.

PCA is a data reduction technique that enables the structure within a large dataset to be examined in order to extract those principal components that identify statistically significant features of variance between waveforms. In essence, PCA reduces a high dimensional dataset into low-dimensional, uncorrelated set of features that maximally explain the variation in the original dataset. These features can then be used to determine between-group differences. To achieve this, PCA arranges correlation coefficients between variables into a correlation matrix. The presence of clusters of large correlation coefficients between variables suggest that these

variables measure aspects of the same underlying dimension. These dimensions are known as components.

PCA was used to extract principal components from the overall data matrix by identifying what combination of variables showed the strongest linear relationship, accounting for as much of the total variance in a dataset as possible. To extract these components, each waveform was transformed into its constituent principal components through eigenvector analysis of the covariance matrix. A singular value decomposition of the covariance matrix was conducted, transforming it into a set of principal components, composed of eigenvectors. These principal components were conceptualised as a set of new variables which are used to describe the original dataset.

It should be highlighted that principal components are abstract statistical entities. They do not indicate which data are related to which principal component. As such they are statistical representations of variance and cannot be interpreted as conceptually real (Portney and Watkins, 2009). When analysing waveforms, the series of principal component coefficients are interpreted as a single mode of variation describing variability within the entire original data set, where each mode is orthogonal to all other modes and ranked in terms of variance via its associated eigenvalue.

Eigenvalues were used to establish a cut-off point to limit the number of principal components for analysis. As eigenvalues represent the amount of variation explained by a factor principal components for each waveform were retained for analysis where eigenvalues were greater than

1.00 and component loadings were greater than > 0.70. Finally, a parallel analysis was used to identify the number of principal components to retain for further comparison. In this manner, only those principal components that captured a greater amount of variability than would be expected by chance were retained for further analysis.

In the present study, normalised gait cycle waveforms for each subject in the early RA and control groups (N= 36) were divided into 101 data time points (0-100%). Each time point corresponded to 1% of the gait cycle from initial contact to on one limb to the next initial contact on the same limb. To perform PCA, the total number of data points should be less than the number of subjects (Field, 2009). For this reason, thirty three data time points (i.e. each alternate data point corresponding to each 3% of the gait cycle) were therefore stored in a 36 x 33 matrix (number of subjects x number of data time points) for 17 kinematic and 9 kinetic waveforms prior to eigenvector extraction. When carrying out PCA, an oblique rotation of the data was performed in order to allow principal components to correlate to component loadings (Field, 2009).

In PCA not all principal components are retained for further analysis. To determine which ones were to be selected, principal components were first evaluated graphically using a scree plot to visually identify the number of components to retain. Group differences in patterns of joint angular joint motion and external joint moments were then evaluated by selecting those principal components which combined accounted for more than 80% of variation in each gait waveform.

When conducting PCA, it is important to assess the nature of the dispersal of correlations within the data. Where partial correlations are present, the pattern of correlations may be too dispersed to allow PCA to be undertaken. To evaluate the dispersal of correlations, the Kaiser-Meyer-Olkin test is used to represent a ratio of the squared correlation to squared partial correlation between variables. This ratio varies between 0 and 1. A value of 0 indicates that the sum of partial correlations is large compared to the sum of correlations. This indicates a diffusion in the pattern of correlations and hence the use of PCA is inappropriate. A value close to 1 indicates a compact pattern of correlations hence PCA is appropriate. Values between 0.5 – 0.7 are considered mediocre, hence values above 0.7 are accepted. In addition, a Bartlett's test of sphericity was used to test whether the diagonal elements of the variance-covariance matrix are equal (i.e. group variances are the same) and that off-diagonal elements are approximately zero (i.e. dependent variable not correlated). Non-significant values indicated that there were no relationships between variables and PCA is not appropriate (Field, 2009).

For each of the waveform variables, between-group differences were examined using principal component scores. Principal component scores represent the transformation of the original observations into a new coordinate space defined by the principal components. Principal component scores provide a measure of distance indicating how closely each waveform conforms to the mode of variability captured by each principal component. Mean Principal component scores were used to illustrate the modes of variance captured for each waveform variable. Since each principal component captures variability across all time points, not all dimensions are required to reconstruct the original data set within a given level of accuracy. Therefore it is possible to reduce the dimensionality of the original dataset matrix and retain only those principal component scores that reflect primary modes of variation. Previous

research by Wrigley et al., (2005) used principal component scores as the dependent variable in order to determine significant between-group differences.

3.10.12 Kinematic coupling

In a biomechanical model, joint rotations are represented by movements taking place between adjacent segments. When movements of two or more body segments are co-ordinated within an overall movement pattern, they are said to be coupled. Kinematic coupling is defined as the angular displacement of one segment relative to the angular displacement of another. Three dimensional angular rotations are calculated by means of transformation matrices and are represented using vectors in relation to the X, Y and Z planar axes (Cappozzo et al., 2005). Whilst providing data on the angular rotations of individual lower limb model segments, a limitation of using vectors is that they can be neither subtracted nor added to one another. It is therefore not possible to analyse the movement patterns that take place *between* segments simply by comparing their adjacent angular rotations. To overcome this limitation, the calculation of intersegmental rotations was carried out using a method presented by Hamill and colleagues known as Vector Coding (Hamill et al., 1999).

The co-ordination of angular rotations between two segments are referred to as *phase relationships*. The *relative* phase is used to identify different states of movement, or co-ordination between adjacent segments. By plotting the angular rotations of a segment against its angular velocity, the 'phase plane' of that segment may be calculated. The difference in phase plane angles between adjacent segments is referred to as the continuous relative phase (CoRP). To provide a continuous measure of segmental coordination throughout the entire

stance phase of gait, between-segment coordination patterns were determined by calculating the continuous relative phase using Microsoft Excel Version 2013. This allowed the assessment of both the flexibility and intrinsic variability in coordination between adjacent segments in early RA participants.

The calculation of the CoRP was described by Hamill et al., (1999). Phase plots were calculated for each joint segment and angle studied. In the first step in calculating the CoRP, phase plots consisting of the angle (θ) on the horizontal axis with its derivative, angular velocity (ω), on the vertical axis were computed. To allow for the calculation of the phase angle (φ), phase plots were normalised for each trial using the following equations:

Horizontal axis (angle): $\frac{2*[\theta i - \min(\emptyset i)]}{\max(\theta i) - \min(\theta i)}$ where Θ indicates the segment angle; *i* indicates the data point within the stance phase

Vertical axis (angular velocity): $\frac{\omega i}{max\{\max(\omega i),\ \max(-\omega i)\}}$ where ω indicates the segment angle; *i* indicates the data point within stance phase

Next, the phase angle was then calculated as follows: $\emptyset = \tan^{-1}\frac{\omega(t)}{\theta(t)}$

The CoRP angle was defined as the difference between the normalised phase angles of adjacent segments throughout stance. The continuous relative phase variability (VCoRP) was calculated according to Miller et al., (2008) as the between stride standard deviation in the continuous

relative phase for a single participant at each time step. VCoRP was averaged over six trials for each subject then averaged across participants.

3.10.13 Study 3: Relationships between early RA walking patterns with measures of disease Activity, disease impact and rheumatology physical function

Functional relationships between the walking patterns of early RA participants and measures of disease activity, disease impact and tests for rheumatology physical function were investigated using regression analysis. This technique is used to determine whether an outcome variable may be either predicted or explained by a single or set of predictor or explanatory variables. This is known as single or multiple regression analysis respectively. Regression analysis was carried out using SPSS Version 22.0.

To avoid the inclusion of misleading or unhelpful variables owing to covariance between data, the selection of which prospective explanatory variables to use was based upon the strength of the Pearson correlation coefficient. Only strongly associated variables entered into the model. In addition, only those variables considered to have a plausible functional relationship based upon evidence presented within the wider rheumatology literature were considered. Once identified, prospective explanatory variables were then grouped into the following categories: measures of disease activity, measures of disease impact, measures of rheumatology physical function, foot posture assessment and temporal-spatial parameters. Variables found to be significantly associated with each principal component score were then entered into a series of linear regression analyses. The model of multiple regression analysis used incorporated a backwards stepwise procedure. This was used to further identify the set of variables that

significantly and independently explained variance in each outcome variable. The outcome variables used for this study were the principal component scores for segmental kinematics that were calculated following PCA.

When conducting a regression analysis, significant correlations between explanatory variables should be avoided as this creates uncertainty regarding the actual strength of association between outcome variables and their predictors. Significant correlations between explanatory variables is known as multicollinearity. The presence of multicollinearity between explanatory variables can increase the variance of coefficient estimates which makes estimates very sensitive to minor change. As a result estimates become unstable and difficult to interpret. Explanatory variables should therefore be selected that avoid multicollinearity within the chosen regression model. When conducting a multiple regression analysis the variance inflation factor (VIF) and its tolerance statistic are used as measures to assess how much the variance of the estimated regression coefficient is inflated by the presence of correlation between explanatory variables. The VIF should preferably be below 1.00 whilst the tolerance statistic should be above 2.0.

In this study, in order to eliminate multicollinearity within the multiple regression models used to explain associations between explanatory variables and 3D gait kinematics, those variables which increased the VIF and tolerance statistic were removed. For each outcome variable, either single or multiple regression analyses were performed depending upon the number of explanatory variables remaining after prior elimination.

CHAPTER 4: Evaluating Test-Retest Repeatability

The reliability of 3D motion capture data may be compromised by errors in instrumentation, investigator fallibility and the inconsistent response of human participants. To test whether the protocols developed for this research were robust enough to allow the aims of this thesis to be achieved, study 1 investigated the repeatability of 3D motion capture and foot posture assessment. The results of study 1 are reported in this chapter.

4.1 Introduction

The presence of extrinsic variability in 3D motion capture data means that their interpretation may in part be determined by the presence of error. Error may occur as a result of the protocols used in undertaking 3D motion capture (Schwartz et al., 2004). Where these data incorporate a high magnitude of error, it is difficult to interpret the true impact of disease on the musculoskeletal function of the foot and lower limb. In mitigating against the impact of error, the approach taken by this thesis was to investigate the magnitude of measurement error within a two phase repeatability study. The following sections report on the results of study 1.

4.2 Aims of Study 1

The aim of study 1 was to establish reliable protocols for the 3D biomechanical evaluation of the foot and lower limb in participants with early RA.

4.3 Study Design

Study 1 used a prospective intra-rater test-retest design to investigate the repeatability of 3D motion capture and foot posture assessment over two phases. Phase 1 investigated the intra-rater test-retest repeatability of 3D motion capture and foot posture assessment prior to the commencement of study 2 and study 3. To ensure that the protocols developed in phase 1 remained robust throughout the duration of the research, phase 2 investigated the intra-rater repeatability of 3D motion capture and foot posture assessment after data collection for study 2 and study 3 had been completed. Figure 4.1 summarises the study design.

4.4 Data Analysis

The repeatability of 3D motion capture data was investigated using two approaches. Firstly, a conventional approach was undertaken using discrete variable analysis. The repeatability of spatial-temporal data was analysed using the following parameters: walking speed (m/s), cadence (steps/min), step length (mm) and stride length (mm). The repeatability of joint kinetics and joint kinematics were investigated using discrete variable analysis of data extracted at the following gait cycle parameters: initial contact, midstance, terminal stance and total joint motion or moment. All discrete variables were analysed using the SEM, ICC, and Bland and Altman 95% LOA. Secondly, a novel approach using waveform symmetry analysis was undertaken. All kinematic waveform data were analysed using waveform symmetry analysis. The following parameters were analysed: trend symmetry, phase offset, range amplitude and range offset. The following The statistical methods used in this study were described in chapter 3 (sections 3.9.4 to 3.9.8). The flow of data analysis in phase 1 and phase 2 of his study is summarised in figure 4.1.

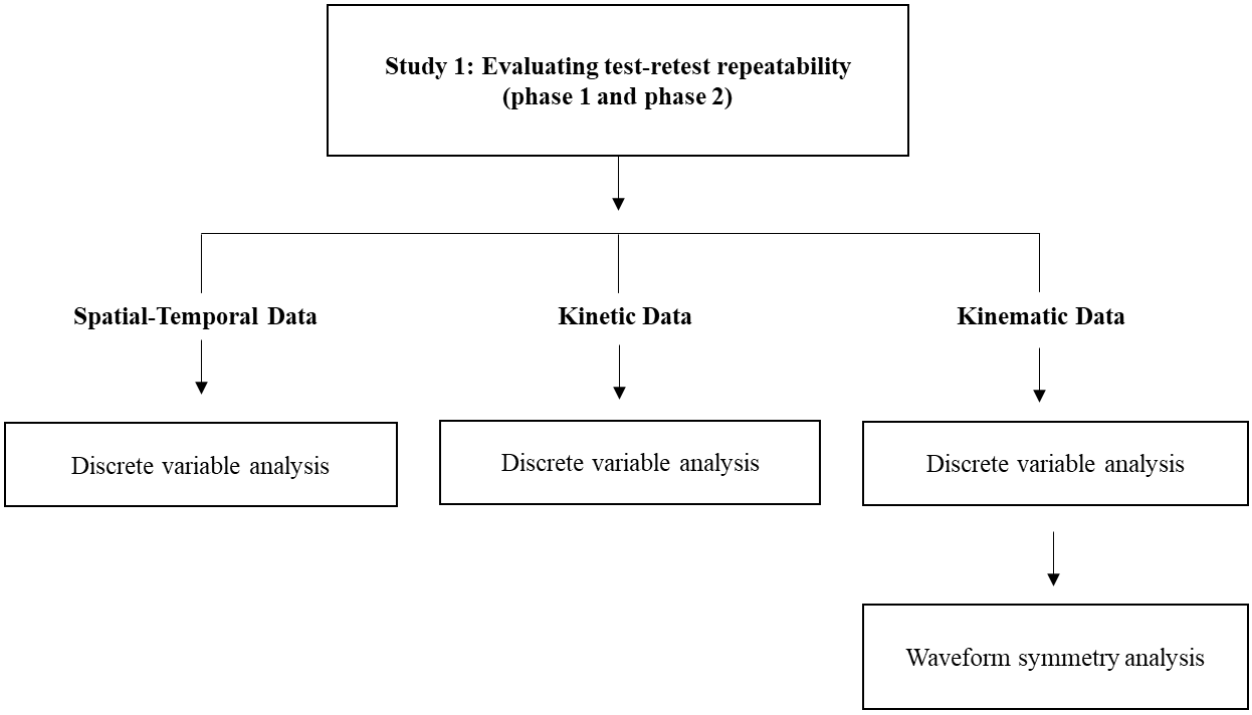

Figure 4.1: Flow diagram of data analysis in study 1

4.5 Participants

Phase 1: Ten participants were recruited for this study, comprising of six control participants (4 males, 2 females, 34 ± 6 years) and four early RA participants (1 male, 3 females, and 45 ± 7 years).

Phase 2: Twenty-five healthy participants were recruited (mean age 44 ± 10 years, male/female ratio 9:16)

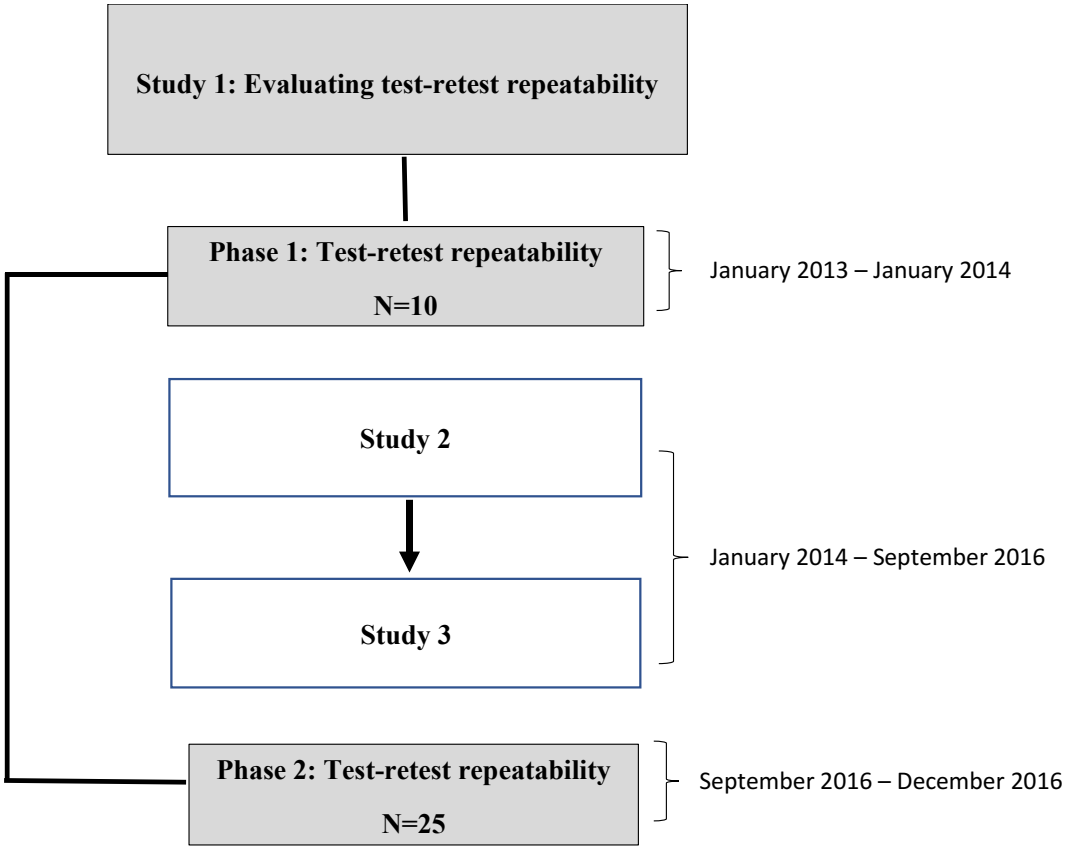

Figure 4.2: Flow diagram of study 1

4.6 Results

This section reports on the results of study 1. Tables A(VI)1 to 12 summarising the results of this repeatability analysis may be found in Appendix VI.

4.6.1 Repeatability of spatial-temporal parameters

Phase 1: Good to excellent repeatability was seen across all spatial-temporal parameters between test 1 and test 2 data. All ICC coefficients for spatial-temporal parameters were observed to be above 0.75 with excellent test-retest repeatability (ICC: 0.90) found in four of the five spatial-temporal parameters analysed. Test-retest variability was least for toe-off (%)

(mean ICC = 0.77, mean SEM = 0.79) and largest for cadence (mean ICC = 0.95, mean SEM = 3.58 steps/min).

Phase 2: Good to excellent repeatability was again seen across all spatial-temporal parameters. All ICC coefficients for spatial-temporal parameters were observed to be above 0.75. With the exception of % foot-off where good repeatability was observed (mean ICC = 0.73), excellent test-retest repeatability (ICC: 0.90) was found for the remaining spatial-temporal parameters analysed. The greatest magnitude of repeatability was observed for cadence (mean ICC = 0.95, mean SEM = 2.58 steps/min).

4.6.2 Repeatability of kinetic parameters

Phase 1: Overall, good to excellent test-retest repeatability (mean ICC: 0.88, mean SEM – 0.05N/Kg) was found for 18 of the 21 kinetic parameters analysed. Test-retest repeatability was lowest at the hip joint (ICC = 0.69, SEM = 0.03 N/kg) and highest at the ankle joint (ICC = 0.96, SEM = 0.02 N/kg).

Good to excellent repeatability was seen in sagittal plane joint moments. The lowest magnitude of repeatability was seen during ankle dorsiflexion (ICC = 0.96, SEM = 0.02N/Kg). The highest magnitude of repeatability was seen at the knee on initial contact (ICC = 0.95, SEM = 0.02N/Kg).

Moderate to excellent test-retest repeatability (mean ICC 0.88, mean SEM 0.01N/Kg) was found for all kinetic parameters in the frontal plane. Test-retest repeatability was lowest at the knee joint (mean ICC = 0.71, mean SEM = 0.01 N/kg) and highest at the hip joint (mean ICC = 0.95, mean SEM = 0.01 Nm/kg). No values of the ICC were below 0.50.

Moderate to excellent test-retest repeatability (mean ICC = 0.81, mean SEM 0.05N/Kg) was found for all kinetic parameters in the transverse plane. Test-retest variability was least at the hip joint (ICC = 0.69, SEM = 0.03 N/kg) and largest at the hip joint (ICC = 0.92, SEM = 0.09 N/kg). No values of the ICC were below 0.50.

Phase 2: Overall, good to excellent test-retest repeatability (mean ICC: 0.85, mean SEM = 0.05 N/Kg) was again found for 18 of the 21 kinetic parameters. Test-retest repeatability was least at the hip joint (ICC = 0.69, SEM = 0.03 N/kg) and largest at the ankle joint (ICC = 0.95, SEM = 0.02 N/kg).

Good to excellent repeatability was seen in sagittal plane joint moments. The lowest repeatability was seen at maximum hip flexion moment (ICC = 0.73, SEM = 0.07N/Kg). The highest repeatability was seen at the minimum ankle dorsiflexion/plantarflexion moment at the ankle (ICC = 0.96, SEM = 0.03 N/Kg).

Moderate to excellent test-retest repeatability (mean ICC 0.81, mean SEM = 0.05 N/Kg) was found for all kinetic parameters in the frontal plane. Test-retest variability was lowest peak hip adduction (mean ICC = 0.69, mean SEM = 0.03 N/kg) and highest at peak hip abduction (mean ICC = 0.96, mean SEM = 0.01 Nm/kg). No values of the ICC were below 0.50.

Moderate to excellent test-retest repeatability (mean ICC = 0.87, mean SEM = 0.01 N/Kg) was found for all kinetic parameters in the transverse plane. Test-retest variability was least at the knee joint (ICC = 0.71, SEM = 0.04 N/kg) and largest at the hip joint (ICC = 0.95, SEM = 0.01 N/kg). No values of the ICC were below 0.50.

4.6.3 Repeatability of Conventional Lower Limb Model

Phase 1: Overall, good to excellent test-retest repeatability was found for 14 of the 15 kinematic parameters analysed in the sagittal plane; (mean ICC = 0.90 and mean SEM = 1.57º). Test-retest repeatability was observed to be lowest at the ankle joint with moderate repeatability observed (ICC = 0.61 and SEM = 2.54°). Repeatability was highest at the hip joint (mean ICC = 0.97, mean SEM = 1.11°). No values of the ICC were below 0.50.

Overall, excellent test-retest repeatability was found for all 15 kinematic parameters in the frontal plane (mean ICC = 0.86 and mean SEM = 0.68 °). Test-retest repeatability was lowest at the ankle joint (ICC = 0.76, SEM = 1.03°) and highest at the knee joint (mean ICC = 0.92, mean SEM = 1.30°). No values of the ICC were below 0.50.

Overall, Moderate to excellent test-retest repeatability was found for 14 of the 15 kinematic parameters in the transverse plane (mean ICC = 0.87, mean SEM = 2.08°). Test-retest variability was least at the knee joint during peak internal rotation (ICC = 0.69, SEM = 2.52º) and greatest at the ankle joint at initial contact (ICC = 0.91, SEM = 0.32°). No values of the ICC were below 0.50.

Phase 2: Overall, good to excellent test-retest repeatability was found for 16 of the 18 kinematic parameters analysed in the sagittal plane (mean ICC = 0.86 and mean SEM = 0.38°. Test-retest repeatability was least at the knee joint at toe-off (ICC = 0.66, SEM = 0.58°) and greatest at the ankle joint at peak plantarflexion (ICC = 0.95, SEM = 0.22º). No values of the ICC were below 0.50.

Overall, excellent test-retest repeatability was found for 17 of the 18 kinematic parameters analysed in the frontal plane; mean ICC = 0.91 and mean SEM = 0.29°. Test-retest repeatability

was lowest at the ankle joint for total range of motion (mean ICC = 0.54, mean SEM = 0.68°) and highest at the knee joint (mean ICC = 0.94, mean SEM = 0.24°). No values of the ICC were below 0.50.

Overall, Moderate to excellent test-retest repeatability was found for kinematic parameters analysed in the transverse plane in stage 1; (mean ICC = 0.83 and mean SEM = 0.38º). Test-retest variability was least at the knee ankle joint for total range of ankle joint motion (ICC = 0.70, SEM = 0.55º) and greatest at the hip joint at initial contact (ICC = 0.96, mean SEM = 0.20º). No values of the ICC were below 0.50.

4.6.4 Waveform symmetry analysis of the Conventional Lower Limb Model

Phase 1: A high level of similarity was seen between kinematic waveforms on trend symmetry analysis. The mean trend symmetry value for all waveforms was 0.99° indicating a high level of symmetry between test 1 and test 2 waveforms. The mean range offset for all kinematic waveforms was 0.23°, indicating similar mean values between test 1 and test 2 measures. The mean range amplitude was 0.97°, indicating that the excursions between waveforms were very similar. All sagittal plane phase shifts were equal to or less than 1%. Trend symmetry was least for frontal plane rotations of the knee with a value of 0.98 and range offset and amplitude of -0.95 and 0.9 respectively. By contrast, symmetry was highest for sagittal plane rotations of the hip with a trend symmetry value of 0.99 and a range offset and amplitude of 0.05.

Phase 2: A high level of similarity was seen between kinematic waveforms on trend symmetry analysis. The mean trend symmetry value for all waveforms was 0.99° indicating a high level of symmetry between test 1 and test 2 waveforms. The mean range offset for all kinematic

waveforms was 0.15 °, indicating similar mean values between test 1 and test 2 measures. The mean range amplitude was 0.89°, indicating that the excursions between waveforms were very similar. All sagittal plane phase shifts were equal to or less than 1%. Trend symmetry was least for frontal plane rotations of the knee with a value of 0. 98 and range offset and amplitude of -0.32 and 0.84 respectively. By contrast, symmetry was highest for sagittal plane rotations of the hip with a trend symmetry value of 0.90 and a range offset and amplitude of 0.04.

4.6.5 Repeatability of the Leardini Foot Model

Phase 1: Good to excellent test-retest repeatability was found for 19 of the 20 kinematic parameters analysed in the sagittal plane, (mean ICC = 0.92, mean SEM = 1.60°). Test-retest variability was least at the first MPJ at peak dorsiflexion (ICC = 0.74, SEM = 5.56º) and largest at the shank-calcaneus (ICC = 0.99, SEM = 0.55°. No values of the ICC were below 0.50.

Moderate to excellent test-retest repeatability (ICC 0.81, 1.90°) was found for 6 of the 10 kinematic parameters analysed in the transverse plane. Test-retest repeatability was least at the shank-calcaneus (ICC = 0.63, SEM = 1.83°) and largest at the calcaneus-midfoot (ICC = 0.86, SEM = 1.26°). No values of the ICC were below 0.50.

Good to excellent test-retest repeatability was found for 9 of the 10 kinematic parameters analysed in the frontal plane, (mean ICC = 0.92, mean SEM = 0.98°). Test-retest repeatability was least at the shank-calcaneus (ICC = 0.72, SEM = 3.10º) and largest at the calcaneus-midfoot (ICC = 0.99, SEM = 0.52°). No values of the ICC were below 0.50.

Phase 2: Good to excellent test-retest repeatability was found for 20 of the 24 kinematic parameters analysed in the sagittal plane (mean ICC = 0.86 and mean SEM = 0.36°). Test-

retest repeatability was lowest at the MLA (ICC = 0.61, SEM = 0.62°) and highest for total range of motion at the shank-calcaneus (ICC = 0.97, SEM = 0.17°). Values of the ICC were below 0.50.

Good to excellent test-retest repeatability was found for 11 of the 12 kinematic parameters analysed in the frontal plane (mean ICC = 0.85 and mean SEM = 0.39°). Test-retest repeatability was least at the calcaneus-midfoot (ICC = 0.90, SEM = 0.32°) and largest at the shank-calcaneus (ICC = 0.68, SEM = 0.57°). No values of the ICC were below 0.50.

Moderate to excellent test-retest repeatability was found for all kinematic parameters analysed in the transverse plane (mean ICC = 0.75 and mean SEM = 0.49°). Test-retest variability was least for total range of motion at the shank-calcaneus (ICC = 0.57, SEM = 0.66°) and largest at the calcaneus-midfoot at initial contact (ICC = 0.90, SEM = 0.32°). No values of the ICC were below 0.50.

4.6.6 Waveform symmetry analysis of the Leardini Foot Model

Phase 1: A high level of similarity was seen between kinematic waveforms on trend symmetry analysis. The mean trend symmetry value for all waveforms was 0.96 indicating a high level of symmetry between test 1 and test 2 waveforms. The mean range offset for all kinematic waveforms was -0.36°, indicating similar mean values between test 1 and test 2 measures. The mean range amplitude was 0.60 indicating that the excursions between waveforms were very similar. All sagittal plane phase shifts were equal to or less than 1% with the exception of sagittal plane motion at the first MPJ which demonstrated a phase offset of 2%. Trend symmetry was least for transverse plane rotations of the calcaneus-midfoot segment with a trend symmetry value of 0.94 and range offset of -3.61. Waveform symmetry was greatest for

shank-calcaneus motion in the sagittal plane with a trend symmetry score of 0.98 and range offset of -0.65.

Phase 2: Symmetry between test-retest waveforms was again found to be high. The mean trend symmetry value for all waveforms was 0.99, indicating a high level of symmetry between test 1 and test 2 waveforms. The mean range offset for all kinematic waveforms was -0.83°, indicating similar mean values between test 1 and test 2 measures. The mean range amplitude was 0.89° indicating that the excursions between waveforms were very similar. All sagittal plane phase shifts were equal to or less than 1%. Trend symmetry was lowest for sagittal plane rotations of the first MPJ with a trend symmetry value of 0.96 and a range offset 0.97. By contrast, symmetry was highest for sagittal plane motion at the MLA with a trend symmetry value of 0.99 and a range offset -2.65.

4.6.7 Repeatability of the Foot Posture Index

In accordance with recommendations by (Tennant and Conoghan, 2007), when conducting Rasch analysis, tests of fit should be undertaken and reported. The results of these analyses for phase 1 and phase 2 FPI-6 raw data are presented in tables A(VI)13 and 17. In both phase 1 and phase 2, Rasch analysis of FPI-6 scores demonstrated good fit to the model across all parameters examined using the criteria described in Chapter 3, section 3.10.9. Person location data were transformed and mapped onto raw FPI-6 scores. Tables A(VI)16 and 17 present the Rasch transformed logit scores for the FPI-6 for all test-retest measures.

Transformed logit scores for phase 1 and phase 2 test-retest measures were analysed using the ICC model (3, 1). An ICC score of 0.85 for this parameter indicated excellent repeatability in

phase 1. Likewise, in Phase 2 excellent intra-rater repeatability was observed with an ICC score of 0.86.

4.7 Discussion

One of the aims of this thesis was to establish reliable protocols for the biomechanical evaluation of the foot and lower limb in participants with early RA. To achieve this aim, study 1 was designed to investigate the intra-rater test-retest repeatability of spatial-temporal, kinetic and kinematic 3D motion capture data. These parameters were investigated using a conventional approach incorporating the analysis of discrete gait variables using the ICC, SEM, mean difference and Bland and Altman 95% LOA. Owing to the limitations of discrete variable analysis, a novel method of investigating test-retest repeatability was undertaken, using waveform symmetry analysis.

When using 3D motion capture for the assessment of musculoskeletal function in the foot and lower limb, it is generally accepted that measurement errors in excess of 5° are not acceptable for clinical decision making (Meldrum et al., 2014). Against this threshold, the magnitude of absolute error reported in both phases of study 1 would be deemed acceptable in both of the 3D biomechanical models tested; most observations of the SEM were below 3°. This suggests that the protocols developed for the use of 3D motion capture within this thesis were robust. In addition to the measurement of absolute error, when the variance of 3D motion capture data were partitioned to allow the analysis of between-participant and within-participant variability, ICC coefficients showed good-to-excellent repeatability across all of the kinetic parameters tested. Good-to-excellent repeatability was also observed in the majority of kinematic data. Intraclass correlation coefficients did however demonstrate a tendency to decrease in value

when kinematic data were analysed at more distally located joints. This would be consistent with the presence of greater magnitudes of variance in motion at these sites. This pattern of increased variability is similar to observations of a proximal-to-distal propagation in error that have been reported in previous studies using the CMC method (refs). In explaining his phenomenon, difficulties in marker placement, soft tissue artefact and errors in joint axis calculation have been proposed as likely factors in the presence of such error (refs).

Overall, sagittal plane joint rotations demonstrated the lowest magnitudes of measurement error with ICC coefficients indicating good-to-excellent repeatability in both 3D biomechanical models tested during phase 1 and phase 2 of the study. In addition, frontal plane rotations also exhibited good-to-excellent repeatability of ICC coefficients. By contrast, transverse plane rotations exhibited more error in repeated measures. Discrete variables exhibiting moderate repeatability were located at the knee and ankle. However, when data from these parameters were analysed across the full duration of the gait cycle using waveform symmetry analysis, a high level of waveform symmetry was observed between test-retest measures. For this reason, these parameters were retained when moving forwards into study 2.

Overall, the results of study 1 suggest that the protocols tested remained robust, with good-to-excellent ICC coefficients sustained across both phase 1 and phase 2. SEM values were generally small and a reduction in the Bland and Altman 95% LOA was observed in several of the parameters tested by the end of phase 2. Taken together, these results suggest that as these protocols became established, the magnitude and range of error of these data showed evidence of an improvement over time.

4.8 Study limitations

There are several limitations to study 1 which arise from issues concerning participant recruitment, study design and the use of multiple comparison procedures. The following section discusses these aspects.

Participant recruitment: Difficulties were experienced in participant recruitment. Whilst it may be argued that the protocols developed for this thesis were robust, the improved repeatability of 3D motion capture data that was observed in this study may in part be due to the small number of participants evaluated in phase 1 (n = 10). It is plausible that this may have contributed to the larger standard deviations and magnitudes of absolute error observed at the beginning of the study. The larger standard deviations and mean difference values for some parameters also suggest that outliers may have accounted for the lower levels of repeatability reported in phase 1. Due to the small numbers of participants recruited for this phase, it was decided not to remove these data from the analysis. The narrower Bland and Altman 95% LOA seen in phase 2 may suggest that the effect of these outliers were reduced as a result of the larger sample size recruited at the end of the study (n = 25).

The availability of a sufficient number of early RA and control participants to attend more than one testing session also prohibited the collection of between-session repeatability data. This limited study 1 to investigating within-session repeatability, rather than incorporating a second between-session repeatability component. Whilst this was in part mitigated by the analysis of a second group of participants in phase 2, it may be argued that this is a limiting factor to the design of study 1. When test-retest repeatability is analysed on the same participants between

sessions that are separated over the course of days or weeks, an increase in the magnitude of error in kinematic data has been reported (Schwartz et al., 2004). It is plausible that fluctuations in disease activity and symptomology in participants with early RA may adversely influence their response to testing with 3D motion capture. Had repeatability testing been performed on the same participants between sessions, greater magnitudes of error may have been observed. Establishing between-session repeatability in early RA participants would have allowed the aims of this thesis to have been achieved within a longitudinal cross-sectional study design. This would be justifiable given that early RA demonstrates a temporal component to the onset and development of musculoskeletal pathology. It may therefore be argued that the limitations in the design of study 1 also had limiting effect upon the overall research design of the thesis.

On the issue of foot posture assessment, the small sample size of participants recruited to both phase 1 and phase 2 of this study mean that the findings for this repeatability analysis should be treated with caution. (Wright and Douglas, 1975) recommend that, in order to have 99% confidence that data stability will measure within ±1 logit, a sample sizes of 50 participants should be used when operating a polytomous Rasch model. This far exceeds the number of participants recruited to study 1. Furthermore, a limitation of the Rasch model is that it may be considered overly prescriptive in that it assumes all items to have equal discrimination. In practice, item discrimination may vary, rendering the measurement tool unequal to the theoretical ideal generated by Rasch analysis. It is therefore unlikely that any dataset will ever demonstrate a perfect data-model fit (Tennant and Conoghan, 2007). This raises the question as to whether the FPI-6 data collected in study 1 provided sufficient quality of measurement for its intended purpose, rather than a matching an unattainable level of theoretical precision. Whilst it may be concluded in this study that foot posture assessment was shown to be

repeatable, difficulties in recruitment do not allow these findings to be generalizable. Furthermore, the utility of the Rasch model means that these findings are not without their conceptual limitations.

Data analysis: Whilst the discrete variables analysed in study 1 represent those conventionally used to investigate repeatability (Rankin and Stokes, 1998), the statistical methods used in discrete variable analysis are not without their limitations. As the ICC is a dimensionless value it is therefore not easily interpreted (Meldrum et al., 2014). In addition, what constitutes an acceptable level of repeatability remains a subjective decision and is generally decided on the basis of the purpose of the instrument under investigation (Steiner and Norman, 2004). A criticism of the ICC is the extent to which it is influenced by between-participant variance. As it measures the ratio of the true score variance to true variance *plus* error, it will invariably be low in conditions where there is little variation among subjects (McDermott et al., 2010). When interpreting ICC coefficients, the value of the reliability coefficient may be considered than whether the magnitude of measurement error renders the instrument practical for clinical use (McDermott et al., 2010). As correlation coefficients like the ICC provide no indication of the magnitude of expected error within repeated tests. As a coefficient of correlation, it is also unitless value. To allow the meaningful interpretation of data the ICC should not be used alone.

To overcome these limitations it is recommended that the ICC ratio is interpreted alongside additional methods of evaluating repeatability which present the magnitude of error in absolute terms using unambiguous units of measurement (Portney and Watkins, 2009). The SEM fulfils this requirement by expressing the correlation coefficient in relation to between subject variance. This method therefore enhances the interpretation of the ICC by providing an indication of the magnitude of the error between repeated tests, whilst also providing an

estimate of absolute error based upon the unit of measurement used in the biomechanical model (Rankine and Stokes, 1998).

As an additional measure, the Bland and Altman 95% LOA provides the range of error that accompanies the absolute measurement of error given by the SEM (Portney and Watkins, 2009). The Bland and Altman 95% LOA is calculated by taking the difference in the mean between two measures, the calculation of the standard deviation of the differences between the two means, then calculating the 95% limits of agreement. Whilst the advantages of this approach are that the 95% limits of agreement provide a range of error that relate to clinical acceptability, this must be interpreted with respect to the range of measures within the raw data.

The analysis of discrete variables may not necessarily represent those time points within the gait cycle at which peak magnitudes of error occur. It is therefore plausible that the magnitude of absolute error that occurred between these discrete variable analysed in study 1 exceeded that considered acceptable for clinical utility. Conventional alternatives of analysing all data points across the kinematic waveform, namely the CMC method, have been shown be affected by a high signal-to-noise ratio (Roislien et al., 2012). To mitigate against this limitation, waveform symmetry analysis was used as a novel approach to the investigation of test-retest repeatability by comparing the shape, amplitude an excursion of kinematic waveforms. Whilst this technique was able to demonstrate that a high level of similarity between test-retest waveforms existed in study 1, it does not specifically measure the magnitude of absolute error. Waveform symmetry analysis therefore cannot be used as an alternative to discrete variable analysis based upon the use of the SEM. Neither does it provide a single correlation coefficient that analyses the between-subject and within-subject variance of data as would be expected

when using the ICC method. Whilst waveform symmetry analysis is used to compare all data points across the kinematic waveform, it is not designed specifically locate where significant differences in the mode of variance of repeatability data may be found within the gait cycle.

Multiple comparison procedures: Finally, it should be acknowledged that whilst the use of multiple test-retest analyses has previously been justified in mitigating against the limitations of individual statistical techniques (Rankin and Stokes, 1998), it is acknowledged that this may increase the likelihood of experiment-wise, or type I error (Gelman et al., 2012). Given the small sample size of participants recruited to study 1, the limitations of the study design and the limitations of the statistical tests used, it cannot be ruled out that multiple testing of these data may have increased the likelihood of concluding that the magnitude of error in repeated measures to be within acceptable limits. However, Armstrong, (2014) advises against the use of multiplicity adjustment procedures such as Bonferroni correction in repeatability analyses on the grounds that that procedures such as the Bonferroni correction are not advisable in circumstances in which variables are highly inter-dependent such as those assessed in study 1. As Bonferroni correction is a conservative procedure, when it is applied to all p values associated with each individual test to maintain the α level over all tests at 0.05, it is possible that the significant between-group differences may go undetected.

4.9 Conclusion

An acceptable level of repeatability was observed in spatial-temporal, kinetic and kinematic data in study 1. These protocols remained robust throughout the duration of the research, showing evidence of an improvement in the magnitude of error by the end of the study. The protocols developed for using 3D motion capture in the thesis were found to be robust enough

to allow the comparative analysis of lower limb biomechanical function in study 2 and study 3.

In the next chapter, these protocols were used to investigate whether spatial-temporal parameters, joint kinetics and joint kinematics in early RA participants are different to age and gender matched healthy controls.

Chapter 5: Comparative Analysis of 3D Motion Capture Data between Adults with Early Rheumatoid Arthritis and Age and Gender Matched Controls

In the second study of this thesis, a comparative cross-sectional analysis was undertaken to investigate spatial-temporal, kinetic and kinematic 3D motion capture data from participants with early RA. To achieve the aims of this thesis, study 2 was conducted over three phases. This chapter presents the results of phase 1 and phase 2 of this study.

5.1 Introduction

In the absence of validated outcome measures for the assessment of musculoskeletal pathologies of the foot and lower limb, researchers have adopted 3D motion capture as a method of collecting data on spatial-temporal parameters, joint kinetics and joint kinematics in participants with early RA. Consistent with the conceptual framework of this thesis, these authors have reported the presence of altered joint kinematics in participants with early RA (Turner et al., 2006; Khazzam et al., 2006; Barn et al., 2013; Gibson et al., 2014). Whilst these studies have documented the magnitude of altered joint kinematics in early RA, from the comprehensive review of the literature, it is plausible that current methods of analysing 3D motion capture data are unlikely to fully elucidate the location, timing and duration of early biomechanical changes in RA. Furthermore, it was argued that the practice of viewing these data as fundamentally linear, or deterministic in nature, may be an additional limiting factor to the interpretation of mechanically based trauma in early RA. With these limitations in mind, the approach taken by this thesis was to extend the work of previous investigators by using

novel approaches in the analysis of 3D motion capture data in the assessment of musculoskeletal pathology in early RA within a three phase study. These approaches were described in chapter 3 (section 3.9.10 and section 3.9.11). The following sections summarise the design of this study and report on phase 1 and phase 2.

5.2 Aims

The aim of study 2 was to quantify and characterize the baseline biomechanical function of the lower limb in adult patients with early RA determining if these characteristics differ from aged-matched healthy adults.

Data from this study was used to answer the first research question of this thesis:

1. When people with early RA are compared to age and gender-matched healthy adults, are there significant between-group differences in the biomechanical function of the foot and lower limb during walking?

5.3 Hypotheses

Data from study 2 was used to test the following hypotheses:

- (H_1) - Lower limb spatial-temporal parameters in adults with early RA will be different from those of age and gender matched adults

- (H_2) - Lower limb joint kinetics in adults with early RA will be different from those of age and gender matched adults

- (H_3) - Lower limb joint kinematics in adults with early RA will be different from those of age and gender matched adults

5.4 Study Design

Study 2 used a comparative cross-sectional study design to compare the spatial-temporal, kinetic and kinematic characteristics of early RA participants against healthy controls using 3D motion capture. To mitigate against current limitations in the analysis of mechanically based trauma in early RA, study 2 was conducted in three phases which are summarised in figure 5.1.

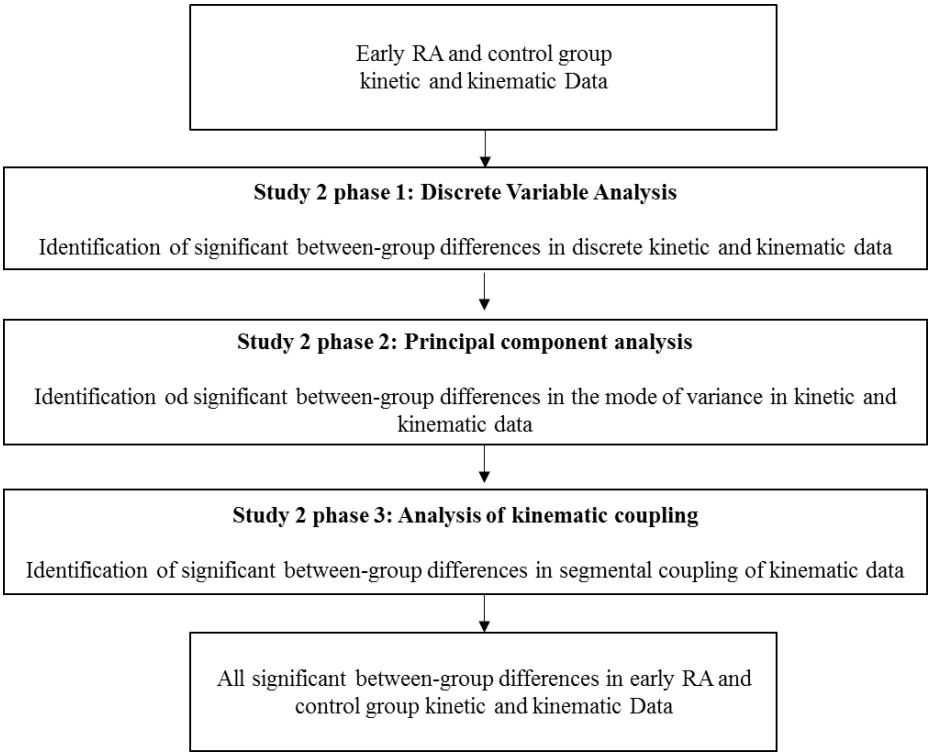

Figure 5.1: Summary of study design

5.5 Data Analysis

In phase 1 of this study investigated the magnitude and significance of between-group differences in spatial-temporal, kinetic and kinematic data using discrete variable analysis. The method of discrete variable analysis used in this thesis was described in chapter 3 (section 3.9.9). To analyse the location, timing and duration of significant between-group differences in 3D motion capture data, phase 2 investigated between-group differences in the mode of variance of kinetic and kinematic data by using PCA. This technique was described in chapter 3 (section 3.9.10). In 3D motion capture data where significant between-group differences were found using PCA, phase 3 investigated the presence of non-linear behaviour patterns in these data by analysing inter-segmental coupling variability. This method is described in chapter 3 (section 3.9.11).

5.6 Recruitment

Early onset adult RA participants were recruited from consecutive outpatient rheumatology clinics. Prospective early RA participants were identified by their rheumatology care teams during out-patient appointments according to the inclusion/exclusion criteria of the study.

A control group of healthy non-RA participants was recruited from a convenience sample of volunteers from local community groups within the Newham, Tower Hamlets, City and Hackney and Waltham Forest areas.

5.7 Participants

A total of 48 early RA participants were referred to the study. Of these, eighteen of the early RA participants recruited (mean age 45.5 ± 9.75 years, male/female ratio 5:13) agreed to provide additional 3D motion capture data. Data from an age and gender matched control group of 18 participants (mean age 43.9 ± 7.58 years, male/female ratio 5:12) were also collected. The flow of early RA participant recruitment for study 2 is illustrated in figure 5.2.

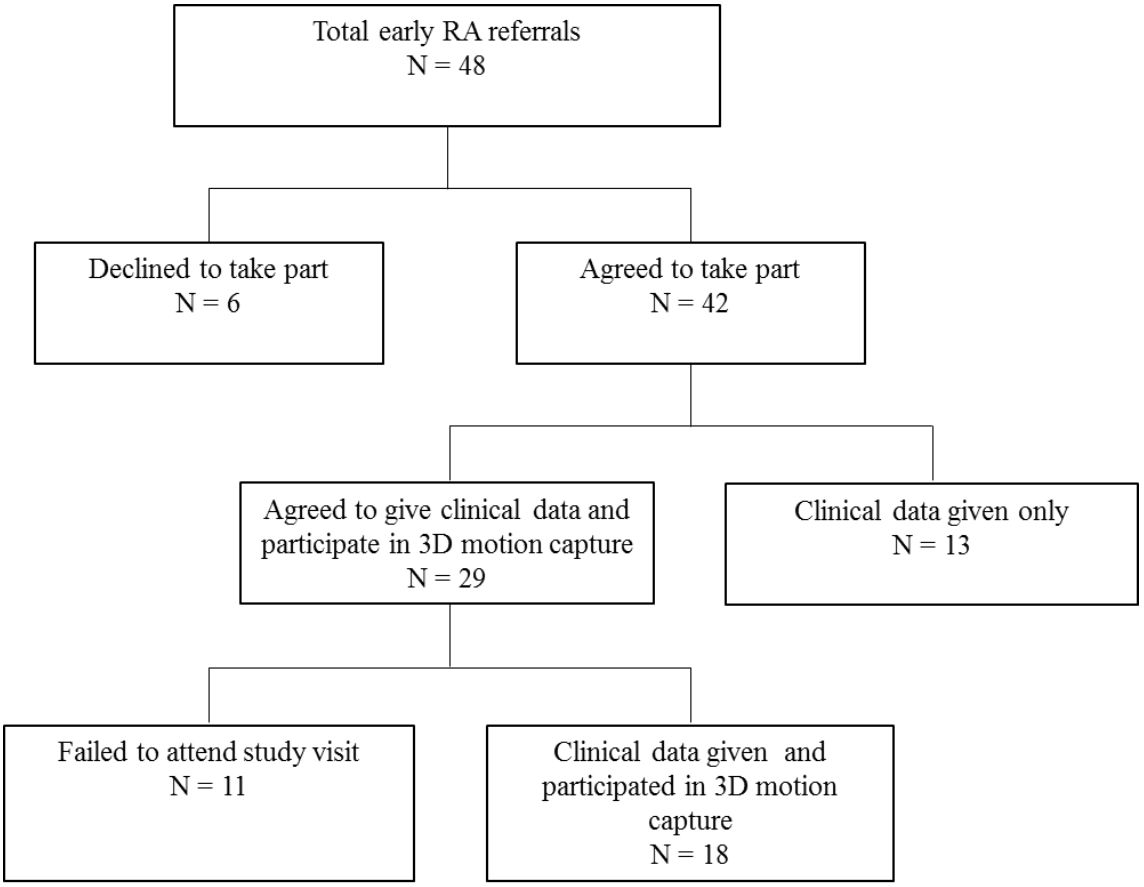

Figure 5.2: Flow diagram of early RA participant recruitment and data collection

5.8 Participant Anthropometrics

Participant anthropometric data are given in table 5.1. No significant group differences in age and gender were found. Significant group differences were seen in height and weight. All data were normally distributed.

Table 5.1: Mean and ± SD of anthropometric data of early RA and control groups evaluated for biomechanical walking patterns

Parameter	*Control Group Mean*	*Early RA Group Mean*	*p-value*
Male: Female Gender	7:11	5:13	
Age (years)	43.90 ± 7.58	45.50 ± 9.75	0.42
Height (cm)	165.55 ± 8.04	**149.61 ± 30.84**	**0.04**
Weight (Kg)	72.15 ± 15.65	**93.94 ± 39. 53**	**0.04**

5.9 Early RA participant demographics

Pharmacological management and self-reported tender joint sites of early RA participants (n=18) are presented in tables 5.2 and 5.3.

Table 5.2: Pharmacological Management of early RA participants (n=18)

Medication	*Frequency (%)*
Methotrexate	72
Sulphsalazine	11
Prednisolone	0
Folic Acid	67
Hydroxychloroquine	11
Cortisone	17
Leflunomide	6
Nil Therapy	11

Table 5.3: Early RA participant self-reported tender joint sites

Joint Site	*Frequency (%)*
Shoulder Joints (%)	25
Elbow joints (%)	0
Wrist Joints (%)	0
Metacarpophalangeal Joints (%)	62.5
Hip joints (%)	0
Knee Joints (%)	0
Ankle Joints (%)	37.5
Subtalar Joints (%)	37.5
Midtarsal Joints (%)	25
Metatarsophalangeal Joints (%)	75

5.10 Results of phase 1: Discrete Variable Analysis

In study 1, discrete variable analysis was used to investigate between-group differences in spatial-temporal parameters, joint kinetics and joint kinematics in participants with early RA compared to healthy controls. The following sections present the results of this analysis.

5.10.1 Spatial-temporal parameters

Spatial-temporal data are presented in table 5.4. All data were normally distributed. Significant group differences were seen in walking speed which was slower in the early RA group (early RA group, 1.10m/s ± 0.17, control group, 1.30m/s ± 1.09) and the percentage of the gait cycle where toe-off occurred (toe-off %) where early RA participants exhibited an increase in the duration of the stance phase (early RA group, 61.09 % ± 1.84, control group, 59.72 % ± 1.33).

Table 5.4: Mean and ± SD of spatial-temporal data of early RA and control groups evaluated for biomechanical walking patterns

Parameter	*Control Group Mean*	*Early RA Group Mean*	*p-value*
Walking Speed (m/s)	1.30 ± 0.09	**1.10 ± 0.17**	**0.00**
Cadence (steps/min)	115.18 ± 8.51	116.02 ± 13.15	0.83
Step length (m)	13.43 ± 24.65	13.01 ± 27.83	0.96
Stride Length (m)	1.35 ± 0.06	1.24 ± 0.22	0.07
Step Time (s)	0.52 ± 0.04	0.52 ± 0.08	0.96
Stride Time (s)	1.04 ± 0.08	1.07 ± 0.13	0.41
Toe-off (%)	59.72 ± 1.33	**61.09 ± 1.84**	**0.02**

5.10.2 Vertical ground reaction force

Vertical ground reaction force data are presented in table 5.5 and figure 5.3. No significant between-group differences were seen in these data. All data were normally distributed.

Table 5.5: Mean and ± SD of vertical ground reaction force data of early RA and control groups evaluated for biomechanical walking patterns

Parameter	*Control Group Mean (N)*	*Early RA Group Mean (N)*	*p-value*
Initial Contact	0.44 ± 0.12	0.34 ± 0.15	0.06
First Peak (F1)	1.63 ± 0.41	1.54 ± 0.50	0.55
Trough (F2)	1.10 ± 0.29	1.07 ± 0.43	0.85
Third Peak (F3)	1.67 ± 0.41	1.57 ± 0.54	0.55
Toe-off	0.44 ± 0.12	0.35 ± 0.21	0.16

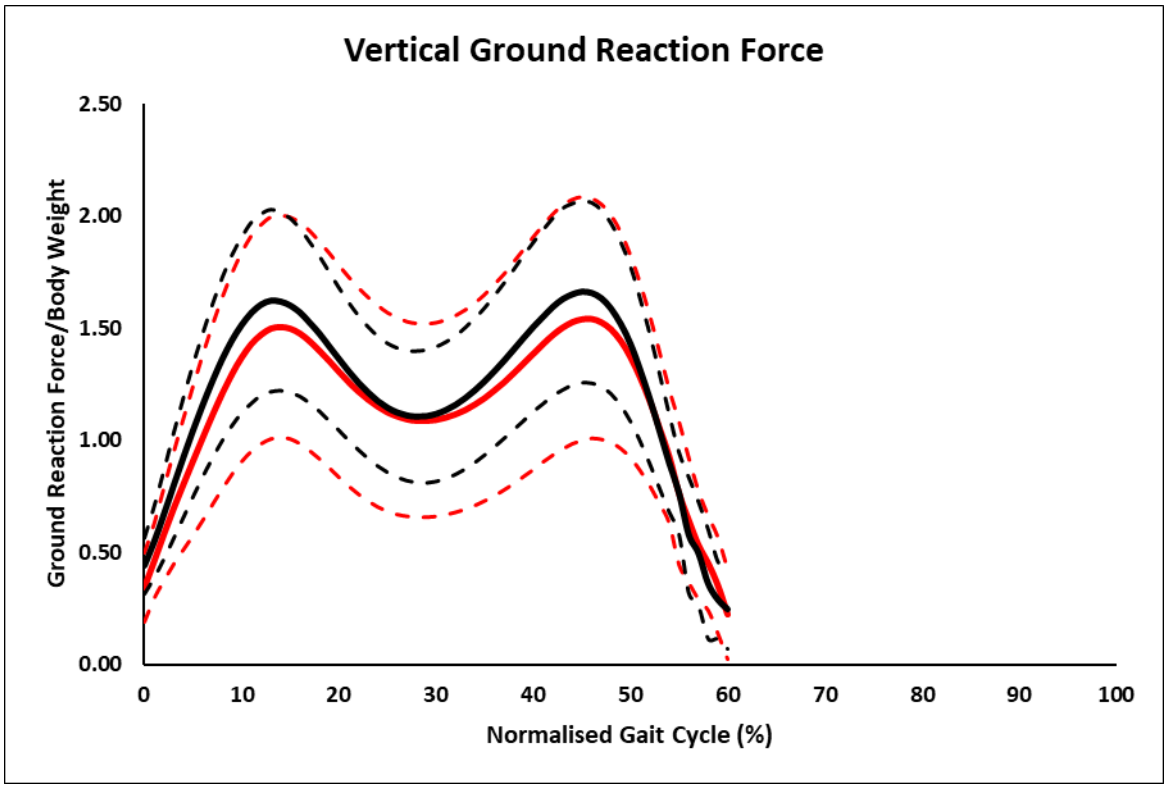

Figure 5.3: Group mean and ± SD vertical ground reaction force data during gait. The black line represents an age and gender matched control group (n=18). The red line represents participants with early RA (n=18). Normalised gait cycle is defined from initial contact of one foot to the subsequent contact of the same foot and is normalised as a percentage. Positive values represent flexion moments. Negative values represent extension moments.

5.10.3 Sagittal joint moments

Mean and SD sagittal joint moment data for the hip, knee and ankle at initial contact, midstance, toe-off, and peak activity are presented in table 5.6. Of these parameters, only data on ankle dorsiflexion at initial contact and peak plantarflexion were found to be significantly different between-groups.

Table 5.6: Mean and ± SD of sagittal plane external joint moments of the hip, knee and ankle in early RA and control groups evaluated during gait

Segment	Parameter	Control Mean (Nm/Kg)	Early RA Mean Nm/Kg)	p-value
Hip	Initial Contact (0%)	0.20 ± 0.21	0.39 ± 0.12	0.11
	Midstance (50%)	-0.64 ± 0.36	-1.31 ± 0.67	0.64
	Toe-off (100%)	0.02 ± 0.12	0.21 ± 0.20	0.84
	Peak Extension	-0.71 ± 0.36	-1.41 ± 0.61	0.66
	Peak Flexion	0.69 ± 0.25	0.75 ± 0.11	0.08
Knee	Initial Contact (0%)	-0.11 ± 0.10	-0.14 ± 0.07	0.11
	Midstance (50%)	-0.05 ± 0.32	0.40 ± 0.43	0.8
	Toe-off (100%)	-0.04 ± 0.04	-0.09 ± 0.06	0.61
	Peak Extension	-0.49 ± 0.12	-0.35 ± 0.15	0.40
	Peak Flexion	0.70 ± 0.38	0.66 ± 0.46	0.21
Ankle	Initial Contact (0%)	-0.09 ± 0.06	**-0.01 ± 0.05**	**0.01**
	Midstance (50%)	1.42 ± 0.22	1.12 ± 0.48	0.21
	Toe-off (100%)	-0.01 ± 0.02	-0.01 ± 0.03	0.72
	Peak Plantarflexion	-0.22 ± 0.11	**-0.13 ± 0.08**	**0.02**
	Peak Dorsiflexion	1.51 ± 0.22	1.19 ± 0.50	0.07

On visual inspection, the ankle joint moment curves of both groups follow a similar motion pattern of initial plantarflexion as GRF moves closer to the ankle, followed by dorsiflexion as

GRF passes in front of the ankle. This rapidly increases following toe-off. Qualitatively, the plantarflexion moment in the first 20% of gait is reduced in the early RA participants. These participants also demonstrated a reduced magnitude of dorsiflexion moment between 25-62% of gait. Between-group differences in ankle joint plantarflexion moments at initial contact were significant with early RA participants exhibiting a reduced plantarflexion moment (Early RA group, -0.01 Nm/Kg ± 0.05, Control Group, -0.09 Nm/Kg ± 0.06). Peak plantarflexion moment was also significantly reduced in the early RA participants (Early RA Group, -0.13 Nm/Kg ± 0.08, Control Group, -0.22 ± 0.11).

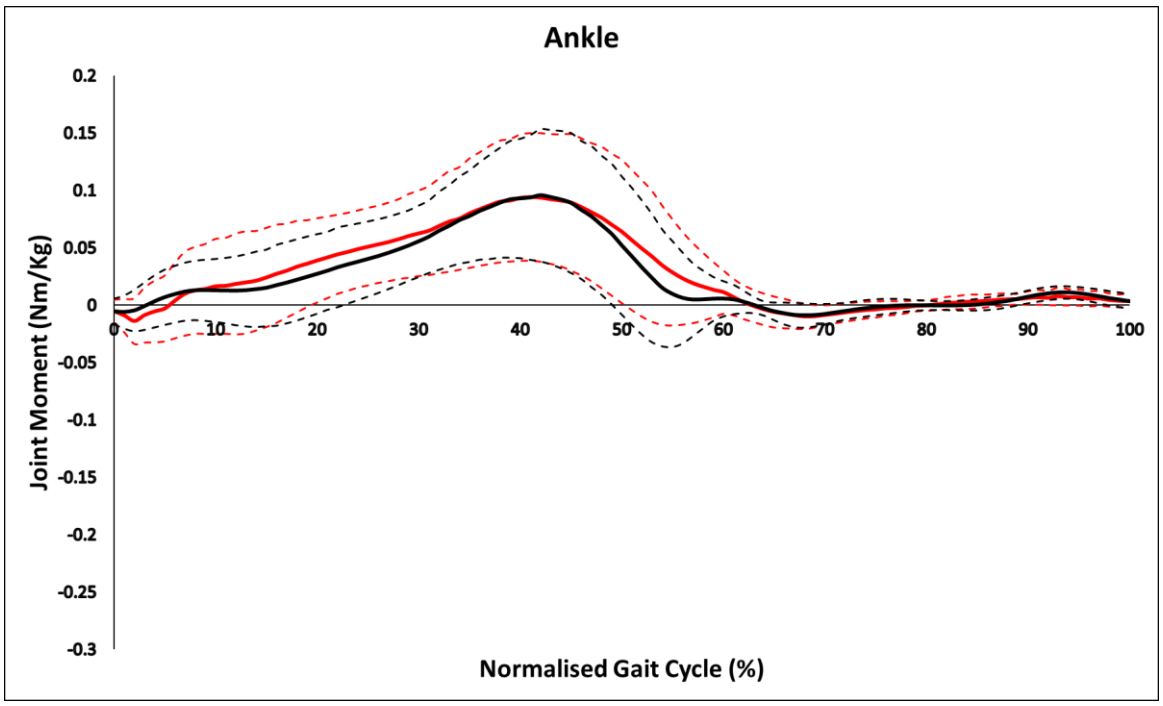

Figure 5.4: Group mean ± SD sagittal plane external joint moments of the ankle during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage. Positive values represent adduction moments. Negative values represent abduction moments.

5.10.4 Frontal joint moments

Mean and SD frontal joint moments of the hip, knee at initial contact, midstance, toe-off and peak activity are presented in table 5.7. No parameter was found to exhibit significant between-group differences.

Table 5.7: Mean and ± SD of frontal plane external joint moments of the hip, knee and ankle kinematics in early RA and control groups evaluated during gait

Segment	*Parameter*	*Control Mean (Nm/kg)*	*Early RA Mean (Nm/kg)*	*p-value*
Hip	Initial Contact (0%)	0.06 ± 0.12	0.04 ± 0.16	0.62
	Midstance (50%)	0.31 ± 0.35	0.41 ± 0.32	0.72
	Toe-off (100%)	0.11 ± 0.09	0.07 ± 0.09	0.07
	Peak Abduction	-0.16 ± 0.11	-0.15 ± 0.09	0.32
	Peak Adduction	0.73 ± 0.32	0.83 ± 0.38	0.64
Knee	Initial Contact (0%)	0.02 ± 0.03	0.06 ± 0.08	0.14
	Midstance (50%)	0.28 ± 0.14	0.26 ± 0.21	0.30
	Toe-off (100%)	0.04 ± 0.03	0.05 ± 0.05	0.71
	Peak Abduction	-0.05 ± 0.02	-0.06 ± 0.04	0.62
	Peak Adduction	0.50 ± 0.18	0.48 ± 0.29	0.99
Ankle	Initial Contact (0%)	-0.01 ± 0.03	-0.01 ± 0.01	0.51
	Midstance (50%)	-0.09 ± 0.03	-0.05 ± 0.06	0.33
	Toe-off (100%)	0.02 ± 0.03	0.02 ± 0.02	0.62
	Peak Abduction	-0.07 ± 0.29	-0.07 ± 0.06	0.74
	Peak Adduction	0.06 ± 0.07	0.06 ± 0.06	0.81

5.10.5 Transverse joint moments

Mean and SD of transverse joint moments of the hip, knee and ankle during walking at initial contact, midstance, toe-off and peak activity are presented in table 5.8. Positive values represent internal rotation moments, whilst negative values represent external rotation moments. No parameter was found to exhibit significant between-group differences.

Table 5.8: Mean and ± SD of transverse plane external joint moments of the hip, knee and ankle kinematics in early RA and control groups evaluated during gait

Joint	*Parameter*	*Control Mean (Nm/Kg)*	*Early RA Mean (Nm/Kg)*	*p-value*
Hip	Initial Contact (0%)	0.00 ± 0.01	0.00 ± 0.02	0.71
	Midstance (50%)	0.04 ± 0.05	0.01 ± 0.07	0.82
	Toe off (100%)	0.01 ± 0.02	-0.01 ± 0.03	0.64
	Peak Ext Rota	-0.13 ± 0.09	-0.16 ± 0.09	0.73
	Peak Int Rota	0.10 ± 0.07	0.09 ± 0.06	0.75
Ankle	Initial Contact (0%)	-0.01 ± 0.01	-0.01 ± 0.01	0.83
	Midstance (50%)	0.04 ± 0.03	0.04 ± 0.04	0.81
	Toe off (100%)	0.01 ± 0.02	0.01 ± 0.03	0.84
	Peak Ext Rota	-0.03 ± 0.02	-0.03 ± 0.02	0.79
	Peak Int Rota	0.11 ± 0.05	0.11 ± 0.05	0.81
Knee	Initial Contact (0%)	0.00 ± 0.01	0.00 ± 0.01	0.87
	Midstance (50%)	0.05 ± 0.04	0.07 ± 0.06	0.30
	Toe off (100%)	0.01 ± 0.02	0.01 ± 0.02	0.76
	Peak Ext Rota	-0.03 ± 0.02	-0.03 ± 0.02	0.89
	Peak Int Rota	0.11 ± 0.06	0.13 ± 0.08	0.34

5.10.6 Sagittal plane kinematics

Mean and SD sagittal plane joint rotations of the hip, knee and ankle at initial contact, midstance, toe-off, peak rotation and total range of motion are presented in table 5.9. Only data on ankle joint dorsiflexion at initial contact and peak plantarflexion were found to exhibit significant between-group differences. Data on ankle kinematics are plotted against the percentage of normalised total gait cycle and presented in figure 5.5.

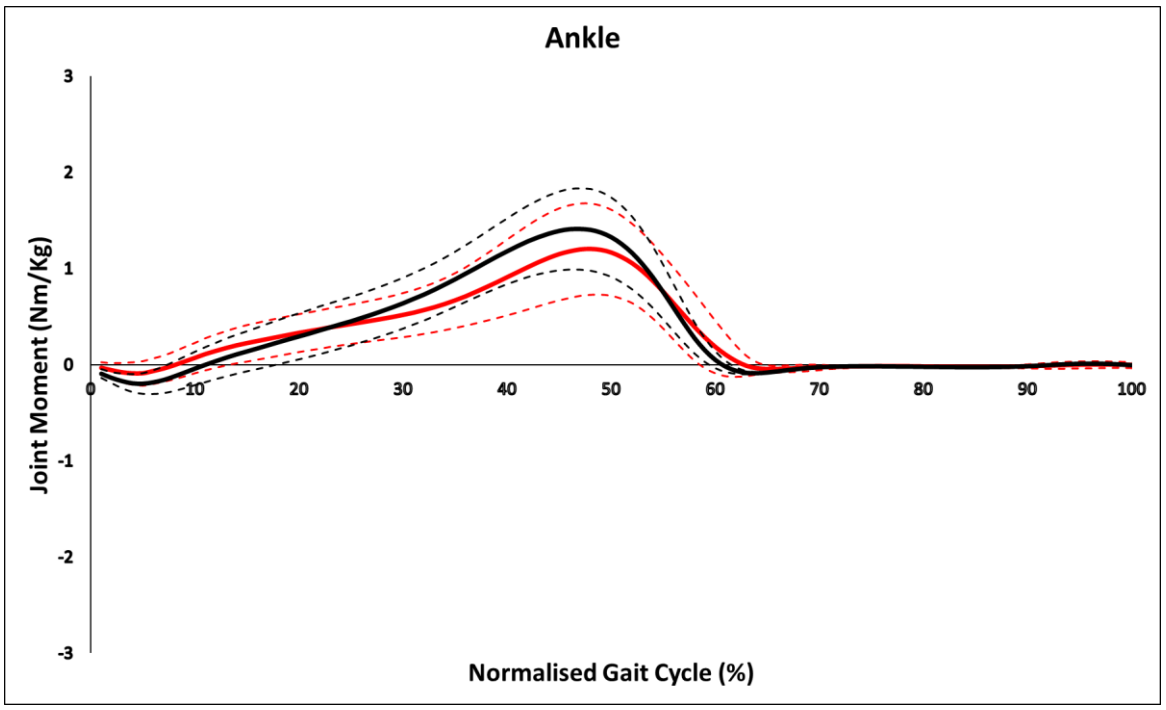

Figure 5.5: Group mean ± SD sagittal plane joint angles of the ankle during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage. Positive values represent flexion values. Negative values represent extension angles.

Table 5.9: Mean and ± SD of sagittal plane joint angles for hip, knee and ankle kinematics of early RA and control groups evaluated during gait

Segment	*Parameter*	*Control Mean (°)*	*Early RA Mean (°)*	*p-value*
Hip	Initial Contact (0%)	34.30 ± 8.34	35.87 ± 6.59	0.34
	Midstance (50%)	-8.82 ± 8.96	-6.18 ± 7.02	0.12
	Toe-off (100%)	33.70 ± 8.73	35.69 ± 6.11	0.29
	Peak Extension	-9.19 ± 8.94	-6.99 ± 6.64	0.32
	Peak Flexion	36.27 ± 8.83	37.61 ± 5.97	0.28
	Range of Motion	45.45 ± 3.25	44.60 ± 5.99	0.53
Knee	Initial Contact (0%)	3.93 ± 4.99	7.74 ± 4.84	0.10
	Midstance (50%)	8.84 ± 6.66	8.78 ± 5.00	0.26
	Toe-off (100%)	3.95 ± 5.32	8.07 ± 4.54	0.14
	Peak Extension	-1.21 ± 5.80	-2.50 ± 4.95	0.17
	Peak Flexion	58.49 ± 5.52	58.40 ± 3.36	0.72
	Range of Motion	59.71 ± 3.04	55.90 ± 5.17	0.27
Ankle	Initial Contact (0%)	-4.60 ± 3.81	-1.45 ± 3.81	0.19
	Midstance (50%)	9.92 ± 4.19	14.95 ± 6.74	0.58
	Toe-off (100%)	-5.27 ± 3.82	**-0.83 ± 2.28**	**0.01**
	Peak Plantarflexion	-21.85 ± 9.09	**-11.88 ± 5.89**	**0.01**
	Peak Dorsiflexion	13.26 ± 3.83	16.09 ± 5.70	0.07
	Range of Motion	35.10 ± 8.86	27.96 ± 8.68	0.10

On visual inspection, angular rotations at the ankle are represented by a quadruple waveform pattern composed of four arcs of motion. The first three arcs occur within the stance phase and consist of: plantarflexion following initial contact; dorsiflexion following full forefoot loading and plantarflexion at the end of the stance phase. The fourth arc represents dorsiflexion of the ankle as foot clearance occurs during swing phase. Visually, both early RA and control group waveforms are similar in shape, following the same overall pattern of motion. Differences can be appreciated visually during the first 10% of gait, with a positive displacement of the early

RA waveform, indicating a reduced magnitude of plantarflexion in these participants from initial contact onwards. From 30% until 75% of the gait cycle the early RA group demonstrate a decrease in plantarflexion and then again between 83% – 100% in late swing prior to the initiation of the next gait cycle. At initial contact, less plantarflexion is seen in the early RA group. By midstance a greater magnitude of dorsiflexion was seen in this group. Significant differences were not however apparent until toe-off where the early RA participants again exhibited less plantarflexion. Maximum dorsiflexion angle was not significantly different (Early RA Group, -5.27 ± 3.82; Control Group, -0.83 ± 2.28). Conversely, minimum plantarflexion angle was significantly different (Early RA Group, -21.85 ± 9.09, Control Group, -11.88 ±5.89).

Mean and SD sagittal plane joint rotations of the shank-calcaneus, calcaneus-midfoot, MLA and first MPJ at initial contact, midstance, toe-off, peak rotation and total range of motion are presented in table 5.8. Significant between-group differences were observed for data on shank-calcaneus, MLA and first MPJ kinematics. These data are plotted against the percentage of normalised total gait cycle and presented in figures 5.6, 5.7 and 5.8.

On visual inspection, a similar quadruple waveform pattern of dorsiflexion and plantarflexion can be observed for the shank-calcaneus which is presented in figure 5.6. Between initial contact and 11% of gait, the early RA waveform is positively displaced indicating a reduction in plantarflexion at this segment compared to the control group. Between 24% and 46% the early RA waveform becomes negatively displaced indicating that early RA participants exhibited less dorsiflexion at this segment. By toe-off, the early RA waveform is again positively displaced. During the swing phase, a negative displacement of the waveform shows

that this group exhibited less dorsiflexion at this segment in preparation for the beginning of the next gait cycle. For this segment a significant between-group difference in plantarflexion at midstance was present (Early RA group, -0.32 ± 3.76, Control group, -1.39 ± 6.67) along with a significant reduction in the overall range of motion (Early RA group, 17.29 ± 3.86, Control group, 24.95 ± 6.41). Significant between-group differences were not present in any other parameter.

Data on MLA kinematics show that both the early RA and control waveforms followed a similar pattern of planar motion in the sagittal plane for this planar angle. The early RA waveform was positively displaced compared to that of the control group. This angle is taken from lines bisecting the longitudinal axis of the rearfoot segment and the first metatarsal. An increase in the magnitude of this planar angle represents a reduction in the height of the MLA as the two reference lines diverge. Conversely, a decrease in this angle results from an increase in the height of the MLA as these lines converge.

Overall, plantar angles for the early RA participants were larger for this parameter indicating a reduction in MLA height. Significant between-group differences were seen at initial contact (Early RA Group, 136.74° ± 12.74, Control Group, 131.38° ± 8.66) and at maximum height representing peak plantar excursion of the MLA (Early RA group, 131.12° ± 10.93, Control Group, 126.71° ± 8.16).

Table 5.10: Mean and ± SD of sagittal plane joint angles for shank-calcaneus, calcaneus-midfoot, MLA and first MPJ kinematics of early RA and control groups evaluated during gait

Segment	*Parameter*	*Control Mean (°)*	*Early RA Mean (°)*	*p-value*
Shank-Calcaneus	Initial Contact (0%)	-3.38 ± 4.49	-3.35 ± 6.08	0.64
	Midstance (50%)	-1.39 ± 6.67	**-0.32 ± 3.76**	**0.04**
	Toe-off (100%)	-3.60 ± 4.29	-2.65 ± 5.62	0.06
	Peak plantarflexion	-19.93 ± 8.22	-13.85 ± 3.58	0.17
	Peak Dorsiflexion	5.01 ± 4.59	3.44 ± 2.02	0.10
	Range of Motion	24.95 ± 6.41	**17.29 ± 3.86**	**0.01**
Calcaneus-Midfoot	Initial Contact (0%)	32.98 ± 10.85	37.57 ± 8.49	0.18
	Midstance (50%)	35.50 ± 9.63	38.64 ± 7.34	0.28
	Toe-off (100%)	32.95 ± 10.53	38.13 ± 8.27	0.23
	Peak Plantarflexion	25.78 ± 10.68	29.90 ± 8.28	0.07
	Peak Dorsiflexion	36.80 ± 9.92	41.24 ± 7.64	0.21
	Range of Motion	11.02 ± 4.45	11.34 ± 4.29	0.17
MLA	Initial Contact (0%)	131.38 ± 8.66	**136.74 ± 12.74**	**0.02**
	Midstance (50%)	131.43 ± 10.16	135.00 ± 9.31	0.06
	Toe-off (100%)	131.47 ± 8.96	137.51 ± 12.41	0.11
	Minimum Height	126.71 ± 8.16	**131.12 ± 10.93**	**0.01**
	Maximum Height	143.38 ± 8.49	148.09 ± 10.34	0.03
	Range of Motion	16.67 ± 4.18	16.96 ± 5.49	0.26
First MPJ	Initial Contact (0%)	43.23 ± 10.91	37.26 ± 9.54	0.06
	Midstance (50%)	41.53 ± 12.24	**33.52 ± 7.40**	**0.02**
	Toe-off (100%)	42.26 ± 11.74	**36.54 ± 9.47**	**0.03**
	Minimum dorsiflexion	78.33 ± 28.97	**66.37 ± 27.12**	**0.01**
	Maximum Plantarflexion	31.39 ± 10.91	**25.02 ± 6.39**	**0.03**
	Range of Motion	46.94 ± 22.37	**41.35 ± 27.88**	**0.03**

At the first MPJ, both the early RA and control group waveforms followed a similar pattern of planar motion in the sagittal plane. The early RA waveform was negatively displaced throughout the gait cycle compared to that of the control group indicating that a lesser

magnitude of dorsiflexion was exhibited by these participants at midstance (Early RA group, 33.52 ± 7.40, Control group, 41.53 ± 12.24) and at toe-off (Early RA group, 36.54 ± 9.47, Control group, 42.26 ± 11.74). The magnitude of maximum dorsiflexion at this joint was also reduced in the early RA group (Early RA group, 66.37 ± 27.12, Control group, 78.33 ± 28.97) as was the total range of motion (Early RA group, 41.35 ± 27.88, Control group, 46.94 ± 22.37).

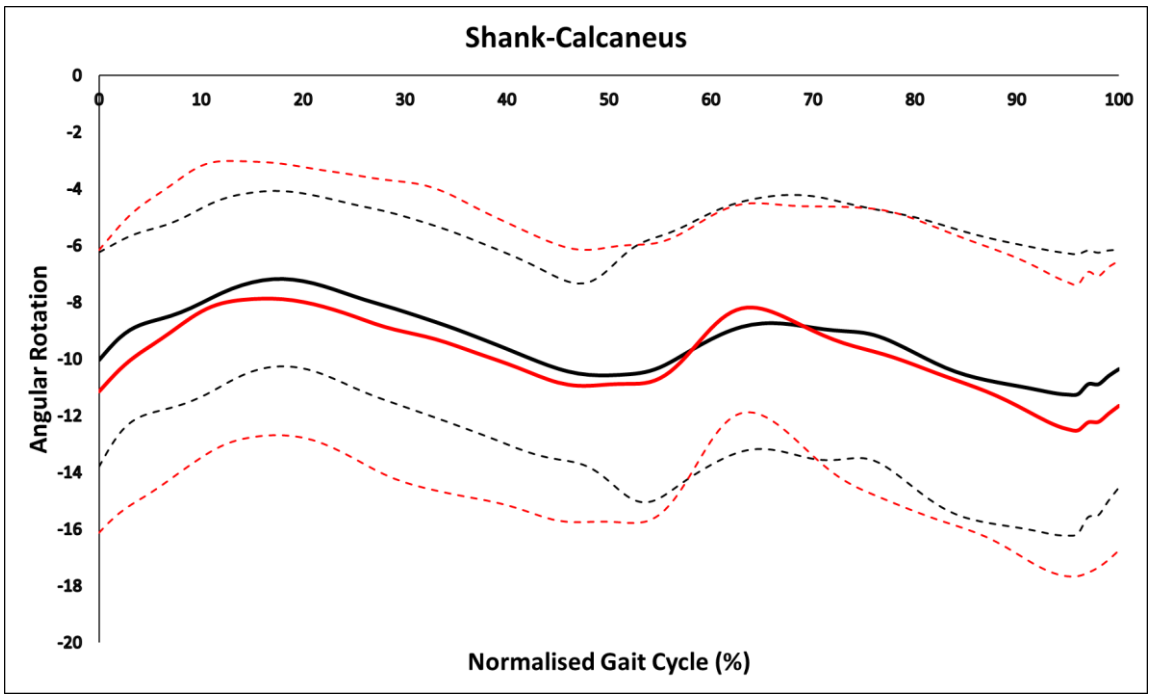

Figure 5.6: Group mean ± SD sagittal plane joint angles of the shank-calcaneus during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage

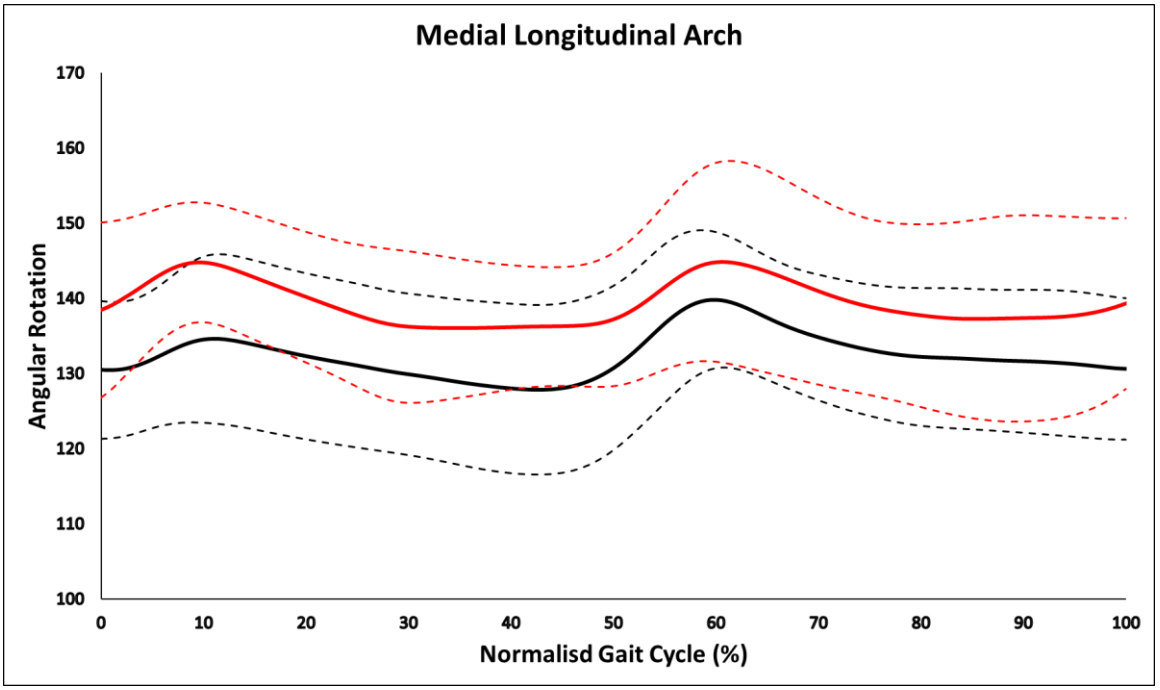

Figure 5.7: Group mean ± SD sagittal plane joint angles of the MLA during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage

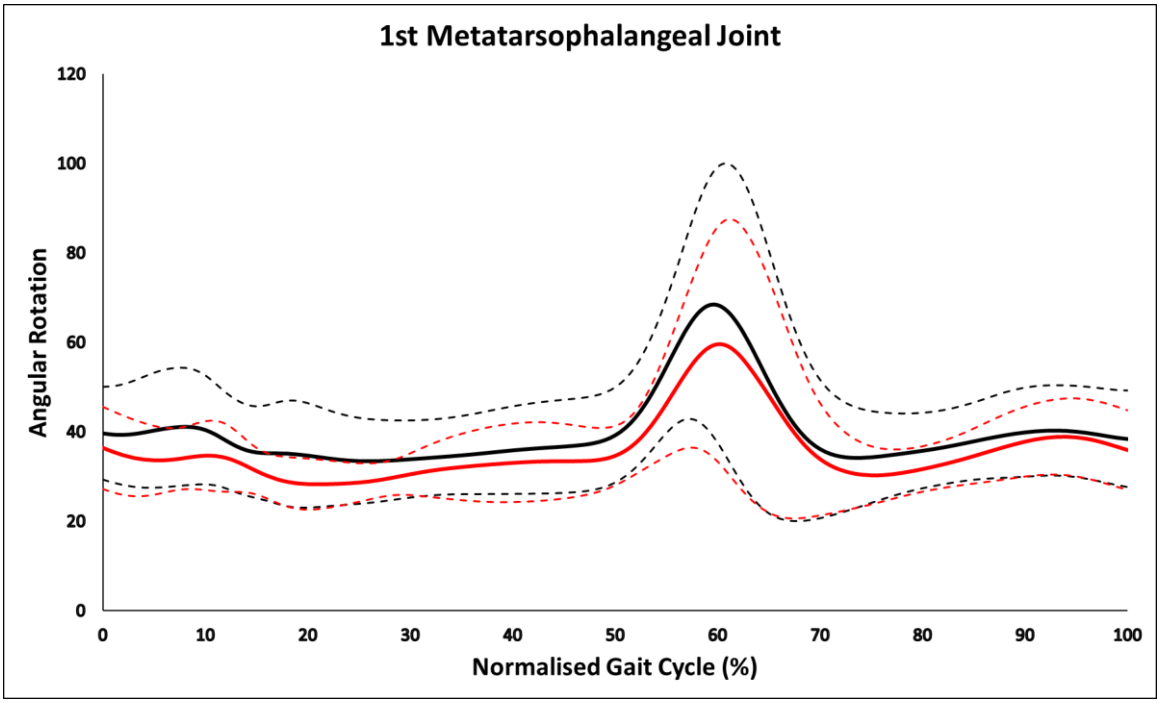

Figure 5.8: Group mean ± SD sagittal plane joint angles of the first MPJ during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage

5.10.7 Frontal plane kinematics

Mean and SD sagittal plane joint rotations of the hip, knee and ankle at initial contact, midstance, toe-off, peak rotation and total range of motion are presented in table 5.11. Only data on hip abduction at toe-off exhibited significant between-group differences. These data are plotted against the percentage of normalised total gait cycle and presented in figure 5.9.

Table 5.11: Mean and ± SD of frontal plane joint angles for hip, knee and ankle kinematics of early RA and control groups evaluated during gait

Segment	*Parameter*	*Control Mean (°)*	*Early RA Mean (°)*	*p-value*
Hip	Initial Contact (0%)	-0.09 ± 4.35	-1.60 ± 3.93	0.97
	Midstance (50%)	0.77 ± 3.77	2.46 ± 3.00	0.73
	Toe-off (100%)	0.18 ± 4.21	**-0.66 ± 3.53***	**0.01**
	Peak Abduction	-7.88 ± 3.47	-5.52 ± 3.50	0.06
	Peak Adduction	8.28 ± 5.40	7.24 ± 2.94	0.30
	Range of Motion	16.16 ± 4.87	12.76 ± 2.39	0.10
Knee	Initial Contact (0%)	-0.33 ± 3.05	-1.20 ± 5.12	0.35
	Midstance (50%)	-1.73 ± 5.00	-2.23 ± 5.07	0.14
	Toe-off (100%)	-0.49 ± 3.20	-1.51 ± 5.23	0.08
	Peak Abduction	-6.35 ± 8.52	-9.76 ± 11.89	0.30
	Peak Adduction	9.63 ± 10.59	3.73 ± 9.23	0.06
	Range of Motion	15.97 ± 6.65	13.49 ± 6.89	0.12
Ankle	Initial Contact (0%)	-1.43 ± 2.59	-1.84 ± 2.59	0.25
	Midstance (50%)	-1.33 ± 2.67	-2.24 ± 1.95	0.11
	Toe-off (100%)	-1.60 ± 2.60	-1.97 ± 2.47	0.29
	Peak Abduction	-2.61 ± 2.52	-3.11 ± 2.30	0.29
	Peak Adduction	2.22 ± 2.76	1.99 ± 2.01	0.31
	Range of Motion	4.82 ± 0.84	5.10 ± 1.20	0.39

Angular rotations at the hip are represented in figure 5.9 by a triple motion waveform curve. On visual inspection both the early RA and control group waveforms follow a similar pattern of motion within a small arc consisting of abduction and adduction. The early RA waveform can be seen however to be negatively displaced for the majority of the gait cycle, indicating a greater magnitude of abduction. Except at toe-off (Early RA Group, -0.66 ± 3.55, Control Group, 0.18 ± 9.21), analysis of the two waveforms did not confirm that the increased magnitude of abduction seen qualitatively was significant

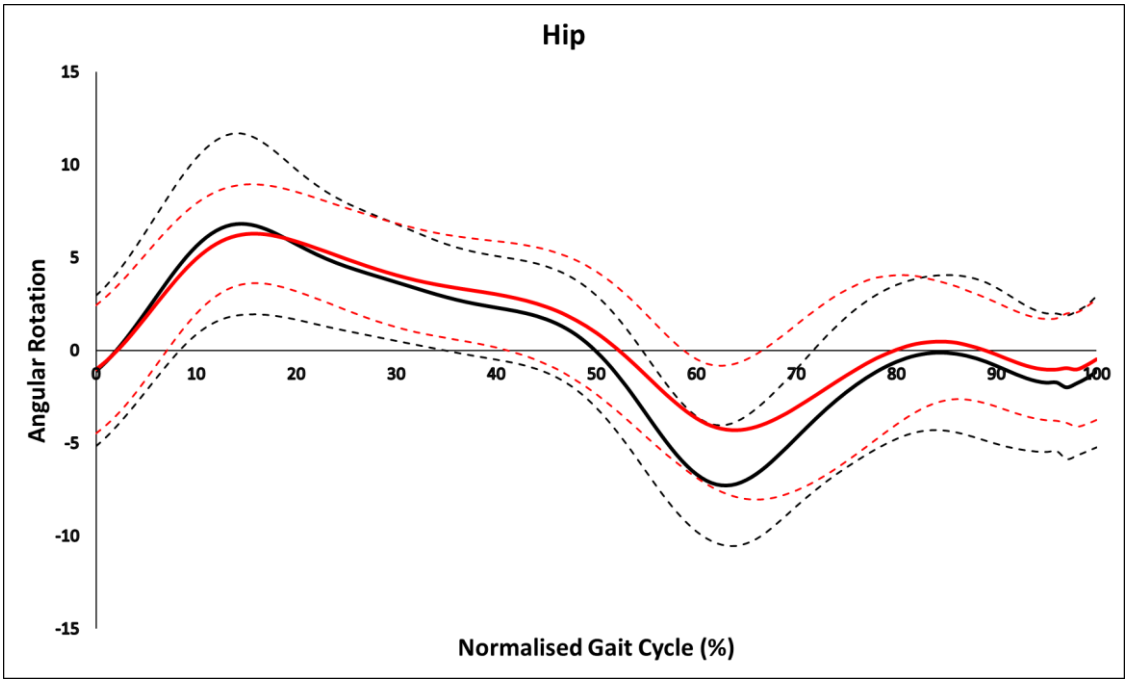

Figure 5.9: Group mean ± SD frontal plane joint angles of the hip during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage. Positive values represent adduction angles. Negative values represent abduction angles

Mean and SD frontal plane joint rotations for the shank-calcaneus, calcaneus-midfoot, MLA and first MPJ at initial contact, midstance, toe-off, minimum rotation angle, maximum rotation angle and total range of motion are presented in table 5.12. Only data on the angular rotation

of the shank-calcaneus at midstance and peak eversion exhibited significant between-group differences. These data are plotted against the percentage of normalised total gait cycle and presented in figure 5.10.

Table 5.12: Mean and ± SD of frontal plane joint angles for shank-calcaneus, calcaneus-midfoot, MLA and first MPJ kinematics of early RA and control groups evaluated during gait

Segment	*Parameter*	*Control Mean (°)*	*Early RA Mean (°)*	*p-value*
Shank-Calcaneus	Initial Contact (0%)	-4.62 ± 4.79	-7.72 ± 5.00	0.09
	Midstance (50%)	-5.53 ± 4.98	**-9.76 ± 5.29**	**0.04**
	Toe-off (100%)	-6.16 ± 5.24	-8.95 ± 5.06	0.35
	Peak Eversion	-9.92 ± 6.79	-10.95 ± 5.69	0.09
	Peak inversion	-2.08 ± 4.37	**-5.35 ± 4.92**	**0.03**
	Range of Motion	7.85 ± 3.30	5.60 ± 2.17	0.11
Calcaneus-Midfoot	Initial Contact (0%)	1.83 ± 6.14	1.02 ± 6.42	0.49
	Midstance (50%)	1.38 ± 5.85	0.49 ± 6.34	0.48
	Toe-off (100%)	1.89 ± 6.20	0.77 ± 6.35	0.58
	Peak Eversion	0.39 ± 5.92	-0.45 ± 6.25	0.47
	Peak Inversion	5.00 ± 6.25	3.18 ± 6.46	0.36
	Range of Motion	4.61 ± 2.61	3.63 ± 1.15	0.37

Both kinematic waveforms illustrated in figure 5.10 follow a similar pattern of inversion and eversion at the shank-calcaneus. Although the early RA waveform is more negatively displaced, both groups operated within an eversion envelope. This indicates that whilst both groups exhibited sustained subtalar joint pronation, the magnitude of the eversion component was higher in the early RA group. Table 5.12 shows that a greater magnitude of eversion was exhibited by the early RA group at midstance (Early RA group, -9.76 ± 5.29, Control group, -5.53 ± 4.98) and at peak inversion (Early RA group, -10.95 ± 5.69, Control group, -9.08 ±

6.79). Significant between-group differences in other parameters for this segment were not found.

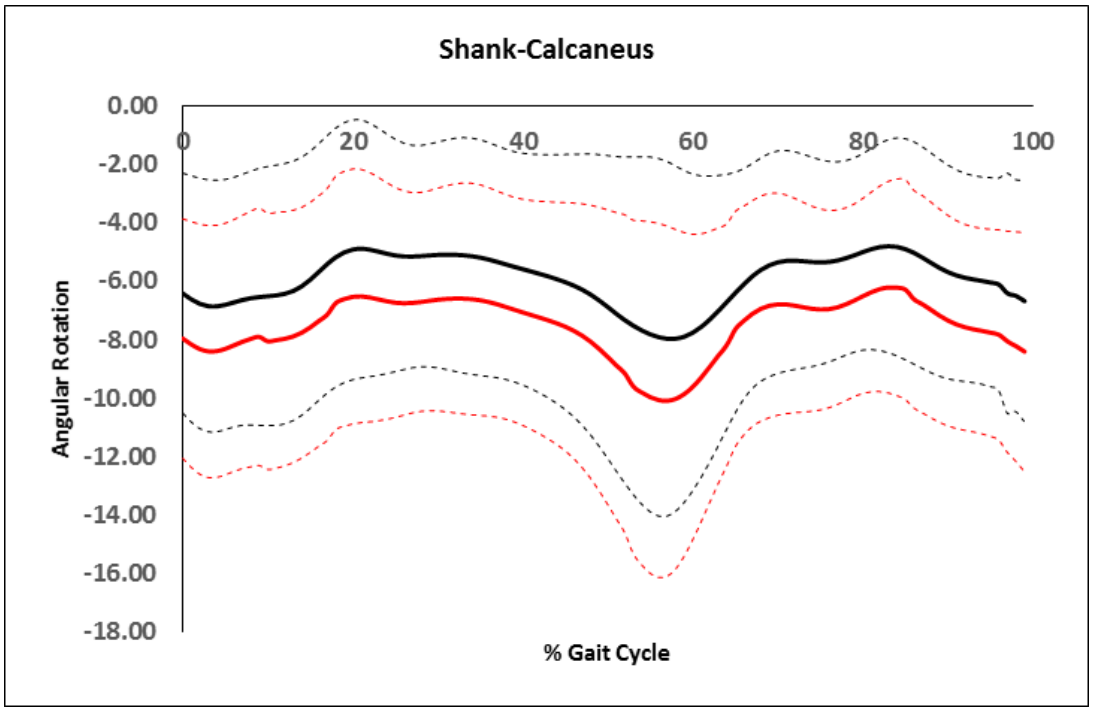

Figure 5.10: Group mean ± SD frontal plane joint angles of the shank-calcaneus during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage. Positive values represent inversion angles. Negative values represent eversion angles.

5.10.8 Transverse plane kinematics

Mean and SD transverse plane joint rotations of the hip, knee and ankle at initial contact, midstance, toe-off, minimum rotation angle, peak rotation and total range of motion are presented in table 5.13. Only data external hip rotation at initial contact were found to exhibit significant between-group differences. These data are plotted against the percentage of normalised total gait cycle and presented in figure 5.11.

Table 5.13: Mean and ± SD of transverse plane joint angles for hip, knee and ankle kinematics of early RA and control groups evaluated during gait

Segment	*Parameter*	*Control Mean (°)*	*Early RA Mean (°)*	*p-value*
Hip	Peak Internal Rotation	-14.24 ± 10.70	-20.21 ± 6.39	0.08
	Peak External Rotation	7.87 ± 11.22	1.99 ± 9.19	0.07
	Initial Contact (0%)	-8.51 ± 9.59	**-16.40 ± 6.02**	**0.03**
	Midstance (50%)	0.34 ± 11.22	-7.93 ± 8.72	0.09
	Toe-off (100%)	-2.27 ± 12.82	-5.48 ± 8.61	0.21
Knee	Peak Internal Rotation	-13.61 ± 10.04	-14.00 ± 6.01	0.40
	Peak External Rotation	6.69 ± 8.29	7.76 ± 5.42	0.73
	Initial Contact (0%)	-8.75 ± 7.85	-8.79 ± 5.09	0.60
	Midstance (50%)	-3.57 ± 9.07	-6.53 ± 7.73	0.77
	Toe-off (100%)	-1.54 ± 10.26	-1.05 ± 7.08	0.87
Ankle	Peak Internal Rotation	-14.79 ± 9.60	-16.76 ± 7.07	0.35
	Peak External Rotation	11.25 ± 8.59	12.56 ± 8.02	0.83
	Initial Contact (0%)	5.57 ± 9.80	3.37 ± 9.71	0.96
	Midstance (50%)	3.96 ± 9.99	8.16 ± 9.50	0.37
	Toe-off (100%)	-1.41 ± 10.16	2.13 ± 10.44	0.55

Kinematic data for the hip demonstrate a similar double internal rotation motion curve in figure 5.11. Both groups exhibit a similar waveform curve with comparable angular excursions and waveform amplitude. From figure 5.10 the hip can be seen to move through an arc of internal rotation followed by a similar arc of external rotation. Angular rotations at the hip were similar at initial contact before moving into neutral rotation. At midstance angular rotations were

similar as were those at toe-off. The hip moved into external rotation by toe-off before internally rotating again during swing. Between-group differences were non-significant.

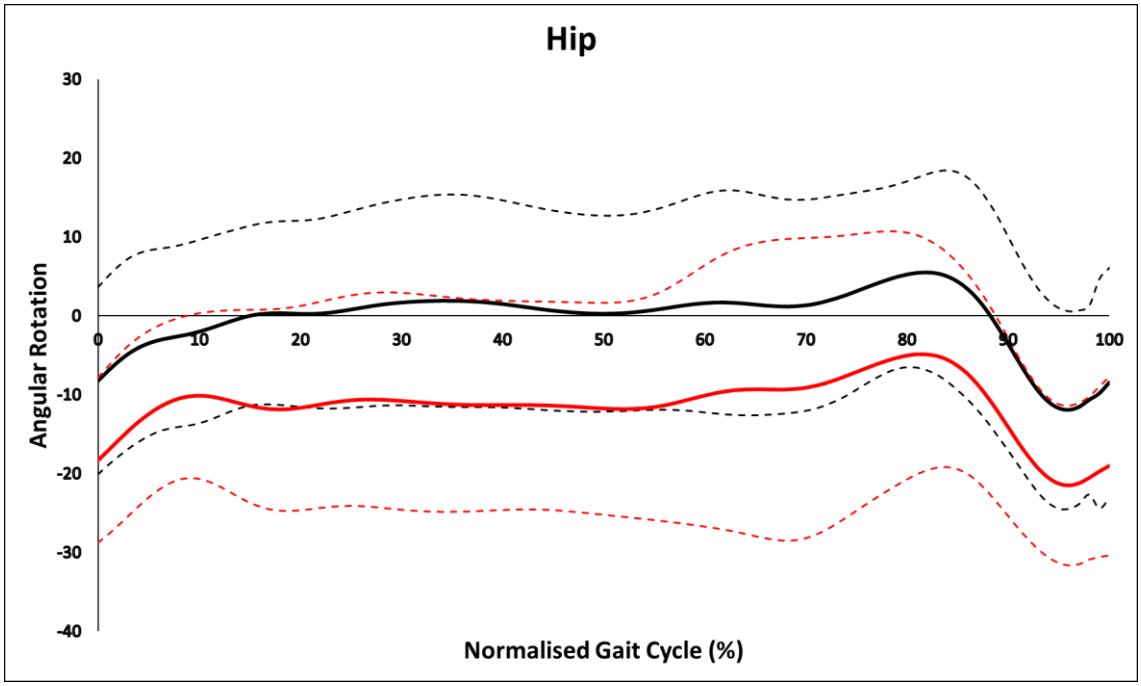

Figure 5.11: Group mean ± SD transverse plane joint angles of the hip during gait. The black line represents the age and gender matched control group (n=18). The red line represents the early RA group (n=18). Normalised gait cycle is defined from initial contact on one foot to the subsequent contact of the same foot. The gait cycle is normalised as a percentage. Positive values represent internal rotation angles. Negative values represent external rotation angles.

Mean and SD transverse plane joint rotations for the shank-calcaneus and calcaneus–midfoot at initial contact, midstance, toe-off, peak rotation and total range of motion are presented in table 5.14. Positive values represent adduction angles whilst negative values represent abduction angles. No parameter was found to exhibit significant between-group differences.

Table 5.14: Mean and ± SD of transverse plane joint angles for shank-calcaneus, calcaneus-midfoot, shank-calcaneus and calcaneus-midfoot kinematics of early RA and control groups evaluated during gait

Segment	*Parameter*	*Control Mean (°)*	*Early RA Mean (°)*	*p-value*
Shank-Calcaneus	Initial Contact (0%)	-10.87 ± 5.16	-11.15 ± 2.59	0.25
	Midstance (50%)	-10.71 ± 4.98	-10.03 ± 3.47	0.33
	Toe-off (100%)	-11.55 ± 5.63	-11.42 ± 2.99	0.51
	Peak Abduction	-13.50 ± 5.00	-13.38 ± 3.05	0.42
	Peak Adduction	-5.96 ± 4.00	-6.56 ± 2.90	0.19
	Range of Motion	7.54 ± 2.20	6.82 ± 2.44	0.39
Calcaneus-Midfoot	Initial Contact (0%)	9.90 ± 4.19	7.25 ± 3.18	0.12
	Midstance (50%)	8.79 ± 4.28	6.54 ± 3.42	0.22
	Toe-off (100%)	9.96 ± 4.11	7.51 ± 3.56	0.31
	Peak Abduction	5.34 ± 3.98	3.59 ± 3.51	0.14
	Peak Adduction	11.34 ± 4.43	9.02 ± 3.28	0.10
	Range of Motion	6.01 ± 1.66	5.43 ± 1.69	0.25

5.10.9 Phase 1: Summary of Findings

- Early RA participants exhibited significantly less plantarflexion at the ankle joint at toe-off. In addition, the minimum angular rotation recorded at this joint was also found to be significantly reduced in early RA participants.

- Early RA participants exhibited less plantarflexion at the shank-calcaneus at midstance. The total range of motion of this segment was also found to be significantly reduced.

- Early RA participants exhibited a significant reduction in the magnitude of peak dorsiflexion at the first MPJ.

- Early RA participants exhibited significant differences in the frontal plane kinematics of the shank-calcaneus at both midstance and for the total range of motion at this segment.

- Early RA participants exhibited significantly less overall motion at the shank-calcaneus. This segment operated within an eversion envelope that was found to be as significantly greater in the presence of early RA.

- Early RA participants exhibited a greater magnitude of eversion at the calcaneus-midfoot compared to that seen in controls.

5.11 Results of phase 2: Principal Component Analysis

In phase 2, PCA was used to investigate between-group differences in the mode of variance in joint kinetics and joint kinematics in participants with early RA compared to healthy controls. The following sections present the results of this analysis.

5.11.1 Sagittal joint moments

Principal component analysis was performed on all sagittal plane hip, knee and ankle joint moment waveforms. Principal component scores are presented in table 5.15. None were found to be significantly different.

Table 5.15: Principal components (PC) and mean ± SD PC score identified for sagittal plane joint kinematic patterns for the hip, knee and ankle in early RA and control group participants during gait

Joint	*Principal Component*	*Control Mean PC score*	*Early RA Mean PC Score*
Hip	PC1	-0.40 ± 3.29	-0.97 ± 2.81
Knee	PC1	1.63 ± 2.43	2.13 ± 3.85
	PC2	-1.10 ± 1.40	-1.13 ± 1.04
	PC3	0.16 ± 0.90	0.10 ± 0.94
Ankle	PC1	1.79 ± 3.62	1.89 ± 4.53
	PC3	0.10 ± 1.12	0.14 ± 1.27

5.11.2 Frontal joint moments

Principal component analysis was performed on all frontal plane hip, knee and ankle joint moment waveforms. Principal component scores are presented in table 5.16. None were found to be significantly different.

Table 5.16: Principal components (PC) and mean ± SD PC scores identified for frontal plane joint kinetic patterns for the hip, knee and ankle in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC score*	*Early RA Mean PC score*	*p-value*
Hip	PC1	12.27 ± 35.26	20.41 ± 31.71	0.36
	PC2	-18.19 ± 31.93	-10.56 ± 20.06	0.28
	PC3	-20.84 ± 29.69	-21.01 ± 28.17	0.98
Knee	PC1	19.74 ± 17	20.01 ± 18.7	0.81
Ankle	PC1	5.13 ± 6.90	5.36 ± 7.18	0.52

5.11.3 Transverse joint moments

Principal component analysis was performed on all transverse plane hip, knee and ankle external joint moment waveforms. Principal component scores are presented in table 5.17. None were found to be significantly different.

Table 5.17: Principal components (PC) and mean ± SD PC scores identified for transverse plane joint kinematic patterns for the hip, knee and ankle in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC Score*	*Early RA Mean PC Score*	*p-value*
Hip	PC1	-0.27 ± 0.66	-0.40 ± 0.78	0.51
	PC2	0.22 ± 0.44	0.11 ± 0.27	0.22
	PC3	-0.01 ± 0.08	-0.02 ± 0.09	0.53
Knee	PC1	0.21 ± 0.31	0.33 ± 0.41	0.19
	PC2	0.22 ± 0.40	0.29 ± 0.52	0.54
	PC3	0.02 ± 0.06	0.02 ± 0.07	0.81
Ankle	PC1	0.11 ± 0.16	0.14 ± 0.22	0.46
	PC2	0.25 ± 0.42	0.28 ± 0.46	0.77
	PC3	0.00 ± 0.09	0.01 ± 0.12	0.70

5.11.4 Sagittal plane kinematics

Principal component analysis was performed on all sagittal plane hip, knee and ankle waveforms. Principal component scores are presented in table 5.18. None were found to be significantly different.

Table 5.18: Principal components (PC) and mean ± SD PC scores identified for sagittal plane joint kinematic patterns for the hip, knee and ankle in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC Score*	*Early RA Mean PC Score*	*p-value*
Hip	PC1	148.03 ± 203.97	209.58 ± 220.25	0.27
Knee	PC1	54.35 ± 105.18	74.17 ± 115.47	0.50
	PC2	143.06 ± 262.37	139.88 ± 258.64	0.96
	PC3	152.43 ± 273.15	164.08 ± 280.11	0.87
Ankle	PC1	1.43 ± 39.19	9.84 ± 40.15	0.42
	PC2	-6.62 ± 38.23	-1.99 ± 31.61	0.62
	PC3	-34.70 ± 79.25	-12.65 ± 47.02	0.20

Principal component analysis was performed on sagittal plane rotations at the shank-calcaneus, calcaneus-midfoot, MLA and first MPJ. Principal component scores are presented in table 5.19. Significant difference were found in principal component scores for the first MPJ. These data are illustrated in figure 5.12.

Table 5.19: Principal components (PC) and mean ± SD PC scores identified for sagittal plane joint kinematic patterns for the shank-calcaneus, calcaneus-midfoot, MLA and first MPJ in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC Score*	*Early RA Mean PC score*	*p-value*
Shank-Calcaneus	PC1	-13.07 ± 56.89	-9.56 ± 54.25	0.81
	PC2	-16.71 ± 65.00	-40.48 ± 49.94	0.12
Calcaneus-Midfoot	PC1	524.44 ± 27.46	527.21 ± 34.55	0.74
MLA	PC1	2102.97 ± 41.58	2100.08 ± 36.62	0.78
First MPJ	PC1	-352.18 ± 45.73	**-416.41 ± 48.86**	**0.00**
	PC2	-43.27 ± 204.59	-55.76 ± 245.97	0.87

Principal component loadings were calculated from data on sagittal plane rotations of the first MPJ in early RA and control participants. Principal components for these data were therefore interpreted to represent the between-group mode of variance in sagittal plane rotations of this segment under the influence of early RA. Three principal components were identified for the first MPJ which combined accounted for 90.15% of the variance of the data between the two groups. The largest mode of variance between groups was captured by the first principal component, PC1. This principal component explained 67.50% of between-group variance. The second principal component, PC2, explained 13.48%. The third, PC3, explained 9.17% of variance. Only PC1 and PC2 were retained following parallel analysis. Principal component scores for these principal components were computed. Significant between-group differences were found for PC1. The mode of variance captured by this principal component occurred between 25% and 89% of the gait cycle with peak variance occurring at 62%. PC1 is illustrated in figure 5.12 against the kinematic waveform for the first MPJ.

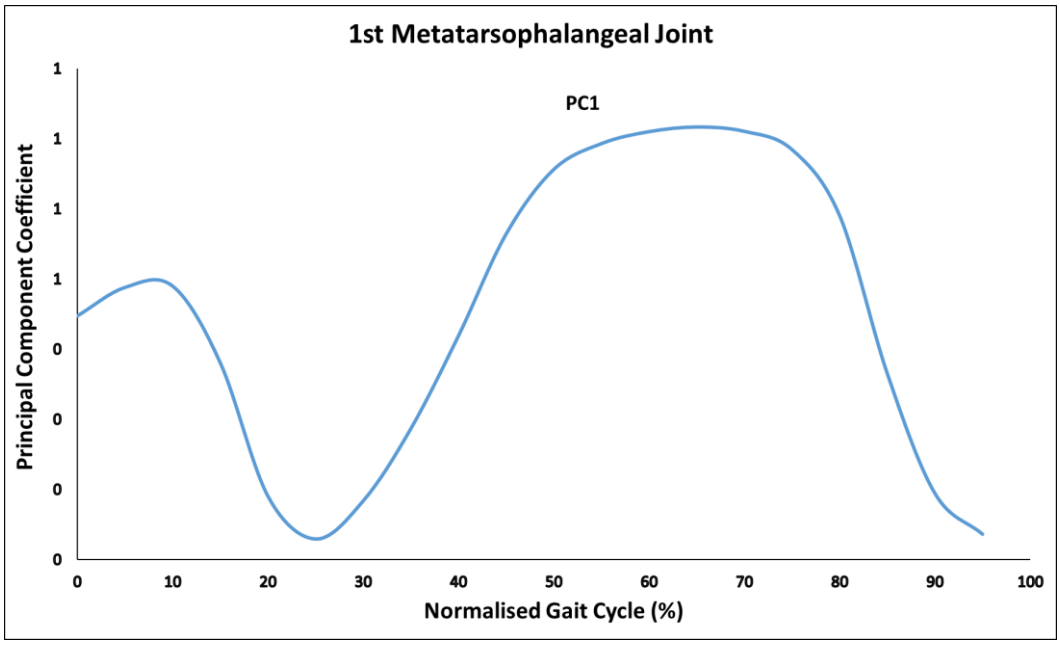

Figure 5.12: Principal component coefficients for sagittal plane joint angles of the first MPJ during gait. The blue line represents principal component plotted against the normalised gait cycle.

5.11.5 Frontal plane kinematics

Principal component analysis was performed on all frontal plane hip, knee and ankle waveforms. Principal component scores for these parameters are presented in table 5.20. None were found to be significantly different. Principal component analysis was performed on shank-calcaneus and calcaneus-midfoot frontal plane waveforms. Principal component scores for these parameters are presented in table 5.21. Principal component scores were found to be significantly different for both segments.

Table 5.20: Principal components (PC) and mean ± SD PC scores identified for frontal plane joint kinematic patterns for the hip, knee and ankle in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC score*	*Early RA Mean PC score*	*p-value*
Hip	PC1	12.27 ± 35.26	20.41 ± 31.71	0.36
	PC2	-18.19 ± 31.93	-10.56 ± 20.06	0.28
	PC3	-20.84 ± 29.69	-21.01 ± 28.17	0.98
Knee	PC1	19.74 ± 17	20.01 ± 18.7	0.81
Ankle	PC1	5.13 ± 6.90	5.36 ± 7.18	0.52

Table 5.21: Principal components (PC) and mean ± SD PC scores identified for frontal plane joint kinematic patterns for the shank-calcaneus, calcaneus-midfoot, MLA and first MPJ in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC Score*	*Early RA Mean PC Score*	*p-value*
Shank-Calcaneus	PC1	-170.13 ± 12.51	**-219.02 ± 9.70**	**0.00**
Calcaneus-Midfoot	PC1	-8.29 ± 6.67	**17.48 ± 7.85**	**0.00**

Principal component loadings were calculated from data on frontal plane rotations of the shank-calcaneus in early RA and control participants. Principal components for these data were therefore interpreted to represent the between-group mode of variance in frontal plane rotations of this segment under the influence of early RA. A single principal component, PC1, explained 91.94% of variance of the data between the two groups for the shank-calcaneus. Parallel analysis of PC1 showed that this principal component explained group differences in variance beyond the possibility of chance. Principal component scores were then computed. Between-group differences in principal component scores for frontal plane motion of the shank-calcaneus were shown to be significantly different. The mode of variance of PC1 is illustrated in figure 5.13. Between-group variance for this segment occurred throughout the duration of the entire gait cycle, peaking at 10% and again at 79%.

Principal component loadings were calculated from data on frontal plane rotations of the calcaneus-midfoot in early RA and control participants. Principal components for these data were therefore interpreted to represent the between-group mode of variance in frontal plane rotations of this segment under the influence of early RA. Frontal plane motion of the calcaneus-midfoot segment demonstrated a single principal component explained 97.57% of the variance between groups which is illustrated in figure 5.14. Principal component scores for PC1 were computed and shown to be significantly different between groups. The variance captured by this principal component is concentrated in two parts of the waveform. The first occurs between 21% and 52% of the gait cycle whilst a second concentration of variability is seen between 76% and 100%. Peak variance was identified at 92%

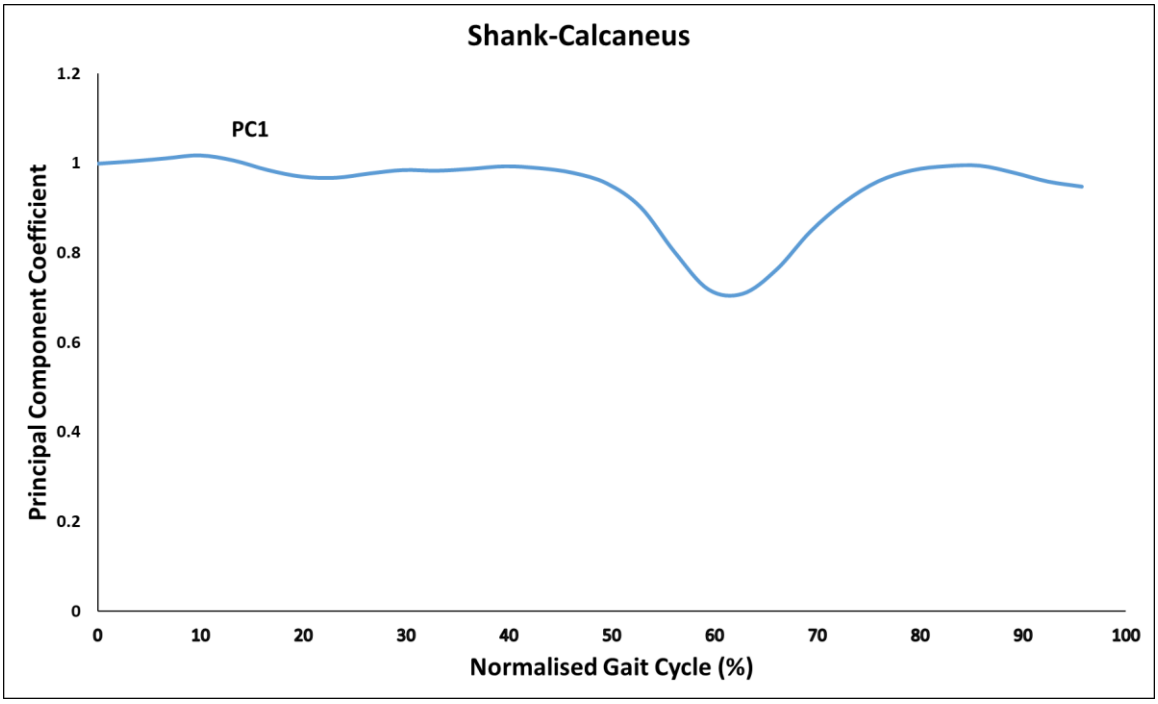

Figure 5.13: Principal component coefficients for frontal plane joint angles of the shank-calcaneus during gait. The blue line represents principal component plotted against the normalised gait cycle.

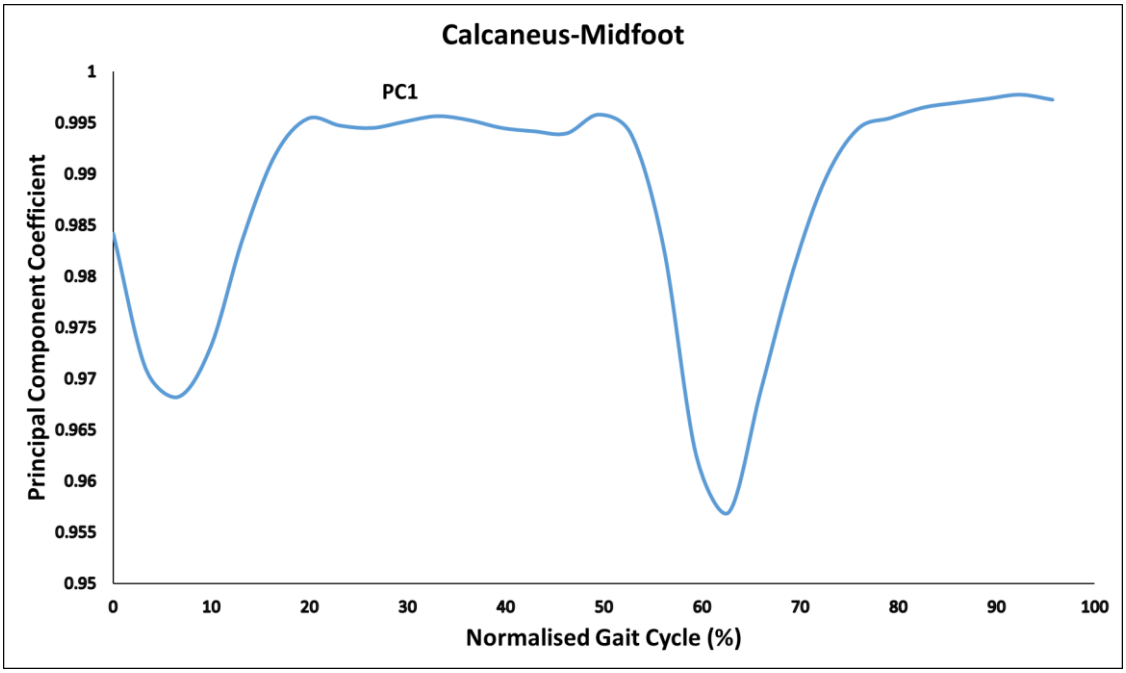

Figure 5.14: Principal component coefficients for frontal plane joint angles of the calcaneus-midfoot during gait. The blue line represents principal component plotted against the normalised gait cycle.

5.11.6 Transverse plane kinematics

Principal component analysis was performed on all transverse plane hip, knee and ankle waveforms. Principal component scores are presented in table 5.22. Only principal component scores for transverse plane data on the ankle demonstrated significant between-group differences.

Table 5.22: Principal components (PC) and mean ± SD PC score identified for transverse plane joint kinematic patterns for the hip, knee and ankle in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC Score*	*Early RA Mean PC Score*	*p-value*
Hip	PC1	-42.80 ± 33.39	-41.50 ± 29.77	0.74
Knee	PC1	11.10 ± 21.10	11.02 ± 20.14	0.82
Ankle	PC1	11.41 ± 24.98	**32.85 ± 48.15**	**0.04**

Three principal components were identified for the ankle, together explaining 98.93% of the variance in these data. Individually, PC1, PC2 and PC3 explained 87.73%, 5.26% and 3.94% of variance respectively. Following parallel analysis only PC1 was retained. Figure 5.15 demonstrates PC1. Principal component scores for PC1 were shown to be significantly different between groups. In PC1 significant between-group variance occurred between 33-52% of gait cycle.

Principal component analysis was performed on transverse plane rotations of the shank-calcaneus and calcaneus-midfoot. Principal component scores are presented in table 5.23.

Principal component scores for both segments demonstrated significant between-group differences. These data are illustrated in figure 5.16 and 5.17.

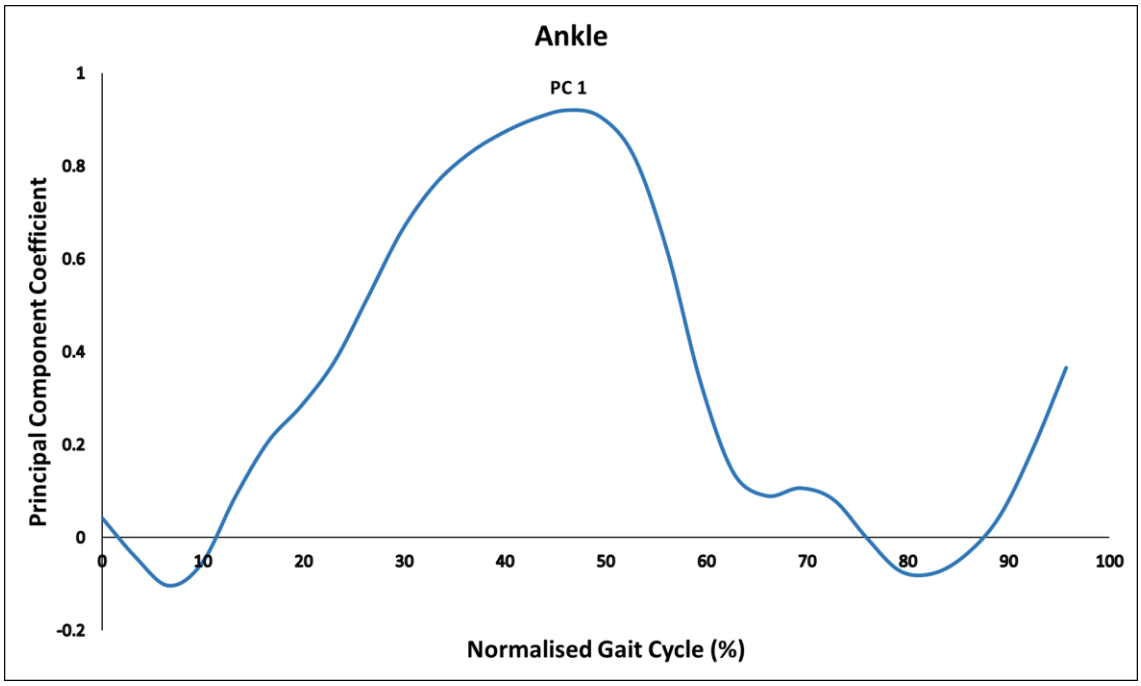

Figure 5.15: Principal component coefficients for transverse plane joint angles of the ankle during gait. The blue line represents principal component plotted against the normalised gait cycle.

Table 5.23: Principal components (PC) and Mean ± SD PC scores identified for transverse plane joint kinematic patterns for the shank-calcaneus and calcaneus-midfoot in early RA and control group participants during gait

Segment	*Principal Component*	*Control Mean PC Score*	*Early RA Mean PC Score*	*p-value*
Shank-Calcaneus	PC1	3.03 ± 63.58	4.06 ± 58.89	0.95
	PC2	-147.74 ± 19.87	**-135.98 ± 18.08**	**0.02**
Calcaneus-Midfoot	PC1	88.84 ± 15.24	**107.27 ± 16.43**	**0.00**
	PC2	3.48 ± 37.71	4.26 ± 45.40	0.94

Two principal components described the major modes of variance for shank-calcaneus segment, interpreted to represent the between-group mode of variance in transverse plane rotations of this segment under the influence of early RA. Combined they explained 95.67% of the variance in data between the early RA and control groups. The first principal component, PC1, explained 80.46% of variance with the second, PC 2, explaining 15.21%. A parallel analysis of these principal components showed that both PC1 and PC2 could be retained for further analysis. Between-group comparison of principal component scores showed that PC1 significantly explained the mode of variance for transverse plane motion at this segment. The greatest variability captured by PC1 was concentrated between 4 - 50% of gait cycle which represents the period of the stance phase following heel strike through to 58%. In PC1 an initial peak in variability occurred at 10%.

PCA identified two major modes of variance for the calcaneus-midfoot, interpreted to represent the between-group mode of variance in transverse plane rotations of this segment under the influence of early RA. Combined the two principal components explained 97.20% of the variance in data between the two groups. Individually, the first, PC1, explained 82.27% of variance with PC 2, explaining 14.93% of variance. Both principal components were retained for further analysis. PC1 was found to be significantly different between-groups with variance taking place between 7-53% of gait cycle, peaking at 10%.

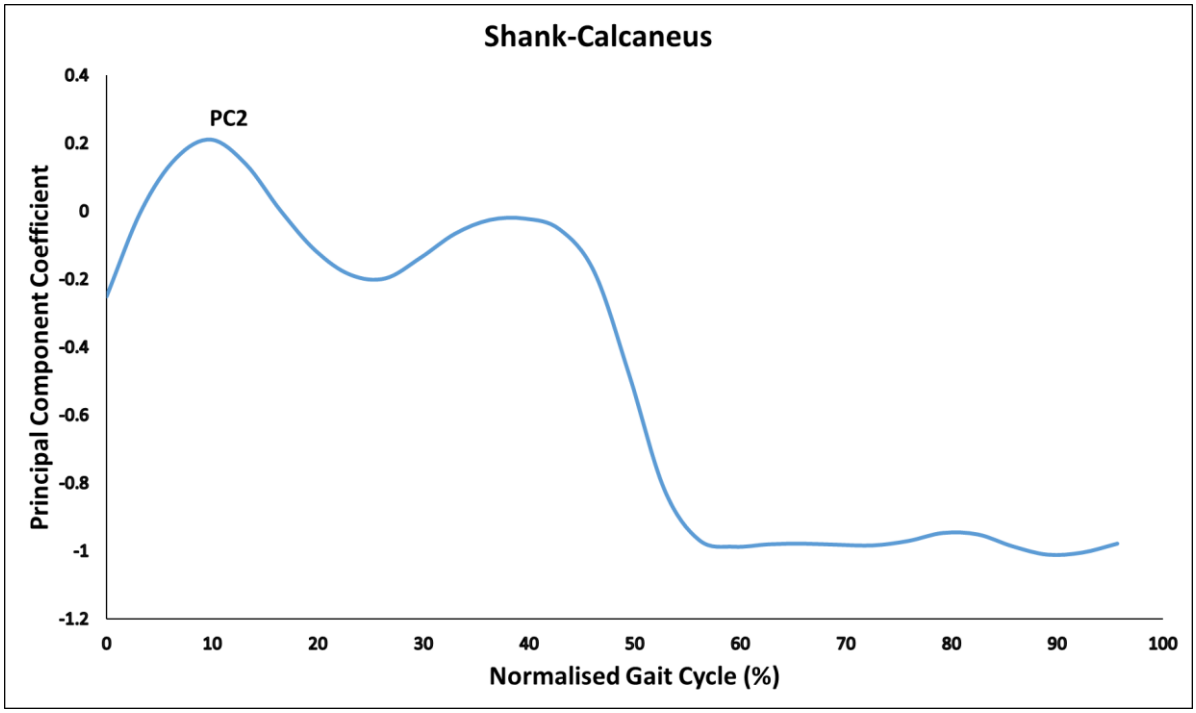

Figure 5.16: Principal component coefficients for transverse plane joint angles of the shank-calcaneus and calcaneus-midfoot during gait. The blue line represents principal component plotted against the normalised gait cycle.

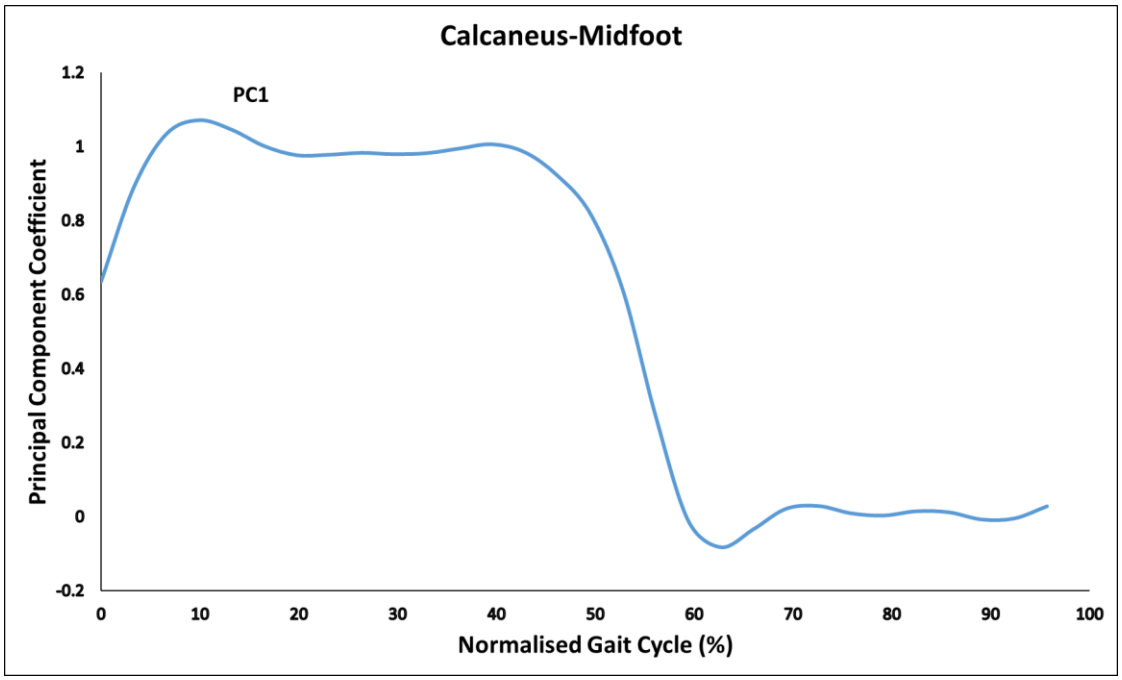

Figure 5.17: Principal component coefficients for transverse plane joint angles of the shank-calcaneus and calcaneus-midfoot during gait. The blue line represents principal component plotted against the normalised gait cycle.

5.11.7 Phase 2: Summary of findings

- A reduced magnitude of dorsiflexion exhibited by early RA participants resulted in significant between-group variance from 25% to 89% of gait. Peak variance in this motion was seen at 62% of the gait cycle, corresponding with the termination of stance.

- PCA showed that the increased magnitude of eversion exhibited by the early RA participants resulted in significant between-group variance throughout the gait cycle, with peak variance taking place in early stance at 10%.

- An increased magnitude of eversion exhibited at the calcaneus-midfoot in the early RA participants was sustained throughout the gait cycle.

- An increased magnitude of internal rotation at the ankle exhibited by early RA participants resulted in significant between-group variance, taking place between 33% of and 52% of gait, peaking towards the end of stance at 55%.

- An increased magnitude of abduction of the shank-calcaneus segment exhibited by early RA participants resulted in significant between-group variance throughout most of stance between 0% and 58% of the gait cycle, peaking at 10%

- An increased magnitude of adduction of the calcaneus-midfoot segment exhibited by early RA participants resulted in significant between-group variance between 0% and 58% of the gait cycle, peaking at 10%

5.12 Discussion

To the best of the authors' knowledge, study 2 is the first to investigate the concurrent segmental kinetics and kinematics of the foot and lower limb in participants with early RA. Following a comprehensive review of the literature, it is believed that this is the first study of its kind to use PCA in determining the timing and duration of significant alterations in the kinetics and kinematics of the foot and lower limb in participants with early RA. The following sections discuss the results of phases 1 and 2 of this study.

5.12.1 Spatial-temporal parameters

Based upon the findings of previous research (Turner et al., 2006; Khazzam et al., 2006; Barn et al., 2013; Gibson et al., 2014), it was anticipated that data on spatial-temporal parameters in participants with early RA would be significantly different to those of age and gender matched controls. Of the parameters analysed in phase 1, two were found to show significant between-group differences. Alterations in walking speed reported in phase 1 (Table 5.4) were found to be similar to those reported by Turner and colleagues who reported this parameter to be reduced to 1.05 m/s ± 0.20. In contrast to the findings of this group, toe-off (%) was also found to be altered in early RA participants. Indicating the termination of stance, this parameter was found to be significantly delayed in early RA participants. In these participants, self-reported pain in the foot and lower limb was observed to be most frequent at the MPJ region (75%) followed by the ankle and subtalar joints (37%). By delaying the initiation of propulsion, loading of the forefoot may have been delayed in these participants to facilitate pain avoidance at these sites. This would be consistent with evidence from plantar pressure studies in patients with established RA (Otter et al., 2008). Alternatively, it is plausible that a delay in terminating

stance may reflect underlying alterations in lower limb kinetics which will be discussed in the next section.

On the basis of these findings, the first hypothesis (H_1) which states that lower limb spatial-temporal parameters in adults with early RA will be different from those of age and gender matched controls, is accepted.

5.12.2 Joint moments

Joint moment data were investigated as they are an indicator of the type of movement brought about by the moments of force acting upon individual joints arising from the product of agonistic and antagonistic muscle activity (Perry, 1992). In phase 1, discrete variable analysis showed that significant between-group differences in peak ankle plantarflexion moments were reduced in participants with early RA. It is believed that this is the first time that this has been reported in early RA. These finding suggest that significant differences in ankle plantarflexion moment data reported in phase 1 may represent an attempt by early RA participants to compensate for weakness in these muscles and to reduce the anterior excursion of the tibia to reduce weight bearing of the metatarsal heads by delaying the onset of forefoot loading. With the tibia advancing forwards upon the weight bearing foot at a slower velocity, heel rise would be delayed. This may explain the observation that walking speed was reduced in early RA participants. This may also explain why the percentage of gait at which foot-off occurred was delayed in this group.

These findings should be interpreted with caution. Vertical GRF data were found to be unaffected by the presence of early RA; a typical double hump vertical ground reaction force curve was exhibited by both groups in figure 5.1 with close similarities in the timing and magnitude of the vertical GRF curves. Data from both groups were also very similar to that reported by Weiss et al., (2008). As external joint moments are calculated by multiplying the external GRF vector by its distance from a joint centre (Richards., 2008), it would be expected that modified external joint moment data would be accompanied by concurrent modifications to vertical GRF. This was not the case in the present study. With between-group differences in principal component loadings for ankle moment data being found to be insignificant, it may be argued that the small sample size of early RA participants recruited to this study may have resulted in type I error (Portney and Watkins, 2009) in phase 1. Alternatively, whilst it is possible that altered muscle function may have played a part in modifying spatial-temporal characteristics in early RA, based upon the results of the findings of phase 2, it is plausible that these parameters were affected primarily by between-group differences in foot kinematics.

On the basis of these findings, the second hypothesis (H_2) which states that hip, knee and ankle kinetics in adults with early RA will be different from those of age and gender matched adults, is accepted.

5.12.3 Segmental kinematics

As a consequence of early RA, it was anticipated that between-group differences in consecutive motions within the foot and lower limb would be observed (chapter 2, section 2.3.13). Whilst significant between-group differences were reported in phase 1, contrary to expectations, the kinematics of hip, knee and ankle kinematics in early RA participants were not found to be

significantly different from controls. The kinematic data reported for both groups of participants reported in tables 5.9, 5.11 and 5.13 were in fact similar to normative values published for these joints (Weiss et al., 2008; Weiss et al., 2009; Beulieu et al., 2007; Kadaba et al., 1999; Perry and Burnfield, 2009). Furthermore, in phase 2, PCA did not detect significant between-group differences in the modes of variance in joint kinematics at these sites in phase 2. Rather, significant between-group differences were reported at the shank-calcaneus, calcaneus-midfoot and first MPJ kinematics. The following section discusses these findings.

Shank-Calcaneus (frontal plane kinematics): The presence of an increased magnitude of peak rearfoot eversion is generally accepted to be a feature of pathological rearfoot motion in RA (Woodburn et al., 2004; Woodburn et al., 2008; Turner et al., 2008). In participants with early RA, this is interpreted to be characteristic of the presence of excessive pronation (Turner et al., 2006). In phase 1, early RA participants were found to exhibit a greater magnitude of eversion at the shank-calcaneus. Discrete variable analysis of frontal plane rotations of the shank-calcaneus in study 1 concur with the findings of Turner et al., (2006). Whilst this group found reported the magnitude of between-group differences in rearfoot eversion to reach -1.1^0, the magnitude of peak eversion observed in phase 1 was more consistent with that reported in established RA. Woodburn et al., (2004) reported peak eversion reach $-7.4^0 \pm 5.1$ in participants with disease of between 6 – 33 years, whilst in the presence in disease of up to 13 years, peak eversion was reported by Turner et al., (2008) to reach $-9.0^0 \pm 7.1$.

Principal component analysis in phase 2 found significant between-group variance in rearfoot eversion. Principal component loadings representing the effect of early RA on shank-calcaneus eversion increased above 0.7 between 0% and 56% of the gait cycle. This mode of variance

incorporates all stance phase events leading up to toe-off, after which principal component loadings reduced below 0.7 from this point onwards. Peak variance in these data occurred at 10% of gait. Comparing figures 5.2 and 5.12, it can be seen that the increase in principal component loadings for this segment correspond to an increase in GRF in response to deceleration of the lower limb following initial contact. Following the termination of stance, eversion of the shank-calcaneus exhibited a second period of variance during the swing phase, extending between early swing (67%) and the initiation of the next gait cycle (100%). Comparisons between figures 5.9 and 5.12 indicate this to correspond to a period of increased rearfoot eversion in early RA participants prior to the onset of the next gait cycle.

Shank-calcaneus (transverse plane kinematics): Discrete variable analysis initially failed to detect between-group differences in transverse plain rotations for this segment. Comparability with previous research is difficult as there appear to be no published data for this parameter in early RA. By contrast, PCA demonstrated significant variance in the transverse plane motion, resulting in principal component loadings above 0.7 from initial contact (0%) onwards. Peak variance for these rotations occurred at 10% of gait with PC loadings reducing below 0.7 until just before midstance (45%). This findings suggest that between-group differences are greatest in the period following initial contact and early weight acceptance of the rearfoot. The major modes of variance in transverse plane rotations of the shank-calcaneus are therefore similar to those of frontal plane rotations of this segment. This would be consistent with the pronatory torque directed towards the subtalar joint by GRF which serves to initiate an abductory component of subtalar joint pronation as part of the weight acceptance and shock attenuation of gait.

Midfoot (frontal plane kinematics): Comparability with previous reports on early RA are difficult as segmental midfoot kinematics have not been investigated before in participants with early RA (Turner et al., 2006; Khazzam et al., 2006; Barn et al., 2013; Gibson et al., 2014). PCA identified two modes of variance within the stance and swing phases respectively. The first mode of variance was seen between 10% and 50% of gait, encompassing motion from early and mid-stance events of gait. The second mode of variance extended from late swing (80%) to the initiation of the next gait cycle (100%). Whilst the increased magnitude of eversion and abduction of the midfoot appeared to reciprocate that reported for the shank-calcaneus, between-group variance in midfoot motion was initiated earlier within stance. This may reflect a proximal to distal propagation of alterations in frontal plane motion between these segments.

Midfoot (transverse plane kinematics): In phase 1, although the magnitude of abduction seen in the early RA group was found to be increased, this was not found to be statistically significant. By contrast, PCA of these data demonstrated significant between-group differences in variance extending between initial contact until 60% of gait, with peak variance in abduction of this segment occurring at 10%.

Medial Longitudinal Arch: Discrete variable analysis showed that MLA height to be significantly lower in early RA participants at initial contact only. The minimum planar angle for this parameter was also significantly lower in the early RA group. Reductions in the height of the MLA were previously reported by Turner et al., (2006) but based upon the calculation of MLA height in millimetres measured from the ground and a tracking marker on the navicular at full forefoot loading. Study 2 found that between-group differences were of a very

low magnitude with a mean difference of -2mm. Due to the small sample size of this study, definite conclusions concerning these findings were not made. Differences in the calculation of MLA height between this study and the Leardini foot model make direct comparisons with Turner et al., (2006) difficult. Furthermore, the mode of variance between groups was not found to be significantly different. From these data, it may be concluded that MLA function appears largely unaffected in participants with early RA participants in contrast to the findings of this group.

First metatarsophalangeal joint: In phase 1, discrete variable analysis of first MPJ motion demonstrated significant between-group differences with early RA participants exhibiting a reduced magnitude of dorsiflexion at midstance, toe-off and peak rotations. To the best of the authors' knowledge, published data reporting on motion at the first MPJ in early RA is lacking. Peak variance in the mode of variability of first MPJ dorsiflexion was found to occur at 60% of gait, corresponding to toe-off. Between-group differences in this mode of variance were, however, found to extend much further. With altered motion at this joint in early RA participants being observed between 40% to 85% of gait, this would be consistent with an overlapping proximal-to-distal propagation in pathomechanical function between the rearfoot, midfoot and first MPJ. These findings suggest that altered function at this joint is initiated much earlier in gait than previous data have suggested (Khazzam et al., 2006) and that this alteration in function is maintained until late within the swing phase.

On the basis of these findings, the third hypothesis (H_3) which states that hip, knee, ankle and foot kinematics in adults with early RA will be different from those of age and gender matched adults, is accepted.

5.13 Limitations of study

There are several limitations to phase 1 (study 1) which may have increased the likelihood of type I error being incorporated into the results of this research. Individually, these limitations arise from the use of multiple comparison procedures, the small participant sample size of study 2 and the use of principal components analysis. This section discusses these limitations.

Multiple comparison procedures: In phase 1 of study 2, gait was partitioned into six variables based upon either specific events (i.e. initial contact, midstance and terminal stance) or the magnitude of segmental rotation (i.e. peak motion and range of motion). It is likely that the probability of finding a significant between-group difference in these data simply by chance (Type I error) exceeded 0.05 owing to the number of variables chosen for analysis (Armstrong, 2014). Subsequent analyses of statistical significance in phase 2 may also have incorporated type I error. As a result, *p* values may have been randomly distributed between 0 and 1 with equal probability, meaning that some are likely to have fallen between 0 – 0.05 (Sainani., 2009).

Reducing the chance of a type I error through multiplicity adjustment procedures such as the Bonferroni correction would, however, have increased the probability of a type II error, i.e. accepting no between-group difference when one exists (Gelman et al., 2012) . In addition, post hoc adjustments such as Bonferroni primarily test universal hypotheses (H_o) which focus on the results of *all* comparisons. This is an approach more commonly associated with confirmatory research (Armstrong., 2014). By contrast, though hypothesis driven, the present research was exploratory in nature (chapter 3, section 3.5); the results of this research cannot be viewed as definitive proof upon which clinical decision making can be made.

Several authors advise against the use of post hoc adjustments in the context of exploratory research (Armstrong., 2014). In addition, multiplicity adjustment procedures do not solve the problem of making valid statistical inferences where the number of analyses are driven in response to data, as was the case in phase 2 of study 2 (PCA) and in study 3 (Linear Regression Analysis). Therefore, as the choice and number of analyses were in effect data dependent, multiple significance tests can only be used for descriptive purposes rather than for clinical decision making, regardless of whether multiplicity corrections have been performed (Bender and Lange., 2001). It has been argued that the as the interpretation of individual tests results is dependent upon the number of tests performed and conclusions should be drawn on this basis and not adjusted (Bender and Lange., 2001).

There is also the possibility that some of the kinematic and kinetic variables analysed were related. This may have had the effect of further increasing the chance of a type I error. To mitigate against this, a Hotelling's two-sample T2 test multivariate analysis of variance (MANOVA) would have been an alternative choice for multivariate analysis. Due to the uncertainty and complexity of meeting the necessary assumptions central to MANOVA analysis (i.e. equivalent linear relationship between variables accompanied by a similar variance / covariance structure), t test based significance testing without multiple comparison procedures was instead chosen.

The results of the present research have been therefore been reported without multiplicity adjustment procedures. On this basis, these results should be viewed as exploratory in nature, in line with recommendations by Portney and Watkins, (2009).

Participant recruitment: A failure to observe significant between-group differences in knee and hip kinematics using discrete variable analysis and PCA in study 2 may be a reflection of the low number of participants recruited for study 2 and the subsequent impact of type II error on the findings of the study. For this reason, the magnitude of between-group differences in kinematic data, particularly for knee and hip may have been underestimated in study 2. If this is indeed the case, the magnitude of between-group differences may have been further reduced as a consequence of normalisation procedures used prior to analysis. Whilst normalisation of kinematic data to the percentage of gait cycle reduces the influence of anthropometric differences on data, time normalisation results in a levelling out of the differences in waveform amplitude, further diminishing of between-group comparisons (Federolf et al., 2013). It may also be argued that the small sample size of study 2 may have led to sampling bias with only the most cooperative and physically able early RA participants volunteering to take part in the research (Portney and Watkins, 2009). Though the recruitment protocols used in this research were designed to minimise bias (Chapter 3, sections 3.3 to 3.5), it cannot be assumed that where significant between-differences in foot kinematics were reported in phase 1 of study 2 that they can necessarily be generalised (Federolf et al., 2013). Importantly, low levels of recruitment may also have resulted in type II error in subsequent analyses undertaken in phase 2 and 3 of this study.

Principal components analysis: The use of PCA in phase 2 may be considered conceptually abstract (Portney and Watkins, 2009). Whilst PCA reduces multidimensional data to its variance component (Chau et al., 2001a), this is at the expense of topological (intrinsic) dimensionality that is indicative of the inherent structures within these data (Chau et al., 2001a). This make the results of PCA difficult to interpret. Numerous factors act in consort to influence the form and magnitude of kinematic waveforms, making these data inherently

multidimensional in nature. Reducing the multidimensionality of kinematic data to unidimensional principal components that represent those underlying dimensions that account for the original set of observed variables is not unproblematic. The utility of PCA rests upon a meaningful post hoc interpretation of these principal components which may introduce subjectivity into the analysis, especially where correlated variables are present as seen in kinematic waveforms (Warmenhoven et al., 2017). The identification of principal components in study 2 was based upon conclusions drawn from the results of between-group analysis in phase 1. These indicated the presence of early RA was associated with increased magnitudes of eversion and abduction at the rearfoot and midfoot as well as reduction in first MPJ dorsiflexion. Whilst it is highly likely that the principal components identified within this study were explained by the presence of early RA, there is also the possibility that these may have alternatively reflected the influence of a yet unidentified explanatory factor. For this reason, it has been argued that PCA can only reveal the global structure of data allowing general, rather than specific conclusions to be made (Chau et al., 2001b).

Based upon previous reports on early RA presented in chapter 5 (section 5.3), the research hypotheses (Chapter 2, section 5.3) reflected an assumption that significant between-group variability in segmental kinematics would be observed when investigated using PCA. It was also considered plausible that physiological complexity secondary to early RA could also act as a contributory factor to between-group differences in foot and lower limb kinematics (chapter 2, section 2.3.4). Whilst PCA was reported in study 2 to show a significant difference in the between-group mode of variance in kinematic data secondary to the presence of early RA, such variability may also have stemmed from both anthropometric differences between participants and differences in motor strategies used to execute gait (Chau et al., 2001b). Furthermore, the multisegmental nature of the lower limb incorporates many degrees of

freedom to create a multidimensional space of motor strategies for the same task (Sparrow et al., 1989). Taken together, this implies that whilst large variation in kinematics is possible, the tolerance for deviation in the complexity of a task such as gait is small (Hamill et al., 1999). It may therefore be argued that large inter and intra subject variation may be present even in the absence of disease activity (Stergiou et al.,2001). As PCA explicitly deals with variances by finding projections aimed at maximising the capture of total variance, large variability in data, regardless of cause, may lead to the identification of false patterns, resulting in type I error (Warmenhoven et al., 2017). For this reason, it cannot be completely ruled out that significant between-group group differences in principal component scores may have been over emphasised by PCA within study 2.

5.14 Conclusion

In the first twelve months following diagnosis, 3D motion capture found evidence of significant alterations in joint kinematics at the rearfoot, midfoot and first MPJ in participants with early RA. These alterations were found despite the presence of low-to-moderate disease activity which was managed using current treat to target DMARD protocols. These alterations were also found to be of a greater magnitude and duration than previously reported.

In the next chapter, the concept of kinematic coupling between adjacent 3D foot model segments is investigated to further test the hypothesis that this the kinematics of participants with early RA are different to those of age and gender matched controls.

Chapter 6: Comparative Analysis of Kinematic Coupling between Adults with Early Rheumatoid Arthritis and Age and Gender Matched Controls

In the second phase of study 2, angular rotations of the ankle, shank-calcaneus and calcaneus-midfoot segments were found to be significantly altered in early RA participants when analysed using discrete variable analysis and PCA. In the third phase of study 2, a dynamic systems approach was used to investigate non-linear behaviour patterns in kinematic data by analysing intersegmental coupling between these segments. This chapter reports on the findings of phase 3.

6.1 Introduction

Investigators have historically viewed 3D kinematic data as the product of deterministic motor behaviours that are predictable and linear in form (van Emmerick et al., 2016). Previous studies of early RA foot kinematics have therefore been based upon the premise that these data are deterministic in nature. It was concluded in chapter 2 (section 2.3.13) that this may not take into account the complex interrelationships between biomechanical and pathophysiological disease processes that together result in what is termed physiological complexity (Van Emmerick et al., 2016). It is therefore plausible that participants with early RA may also exhibit non-linear behaviour in foot kinematics that may contribute to the pathogenesis of mechanically based musculoskeletal pathology (Van Emmerick et al., 2016). Analysing the co-ordination variability of angular rotations between those 3D biomechanical model segments that were found to exhibit significant between-group alterations in their kinematics in phase 2 may further elucidate the pathogenesis of mechanically based trauma in early RA.

In phase 1 and phase 2 of this study, 3D motion capture data of the foot and lower limb were investigated. Significant between-group differences in the magnitude of segmental kinematics of the shank-calcaneus and calcaneus-midfoot were reported. In phase 2, PCA found these segments to also exhibit significant between-group differences in their mode of variance. To determine whether the inter-segmental coupling between these segments exhibited non-linear behaviour patterns as an additional source of mechanically based trauma, these segments were carried forward for further analysis in phase 3 of this study. Phase 3 investigated inter-segmental coupling between the shank (which is analogous to the lower leg) and the shank-calcaneus (which is analogous to the rearfoot). Inter-segmental coupling between the shank-calcaneus and calcaneus-midfoot was also investigated. This chapter reports on the results of these analyses.

6.2 Data Analysis

The analysis of kinematic coupling was described in Chapter 2 (section 3.8.11). This technique involves plotting the angular rotations of a segment against its angular velocity, in order to calculate the phase plane of that segment. The difference in phase plane angles between adjacent segments is referred to by Hamill et al., (1999) as the CoRP. Using the CoRP, the phase relationship between adjacent segments and their variability component (VCoRP) may be described throughout the duration of a movement task. In this manner, transitions in the coordination pattern between 3D biomechanical model segments were characterised.

Using the method described by Hamill et al., (1999). Coordination patterns were analysed according to whether they were either in-phase or out-of-phase. In-phase coordination patterns

represent intersegmental rotations that move in the same direction. Conversely, out-of-phase coordination patterns represent intersegmental rotations occurring in opposite directions. In addition, coordination patterns with a negative displacement indicate that the distal segment rotated to a greater magnitude compared to the proximal segment. The converse is true where coordination patterns are positively displaced.

6.3 Hypothesis

Phase 3 of study 2 was designed to test the third hypothesis of this thesis:

- (H_3) - Lower limb joint kinematics in adults with early RA will be different from those of age and gender matched adults

6.4 Study Design

In a comparative cross-sectional study of eighteen early RA participants and eighteen age and gender matched controls, kinematic coupling between the shank-calcaneus and calcaneus-midfoot was investigated by analysing between-group differences in coordination variability using the VCoRP. Participant anthropometrics and disease activity have already been described in chapter 5 (section 5.7). Figure 6.1 illustrates phase 3 of this study.

6.5 Results

The mean CoRP and VCoRP data for early RA and control group participants are presented in table 6.1. The following sections report in details the kinematic coupling patterns investigated within phase 3 of the study.

Figure 6.1: Analysis of kinematic coupling variability in phase 3

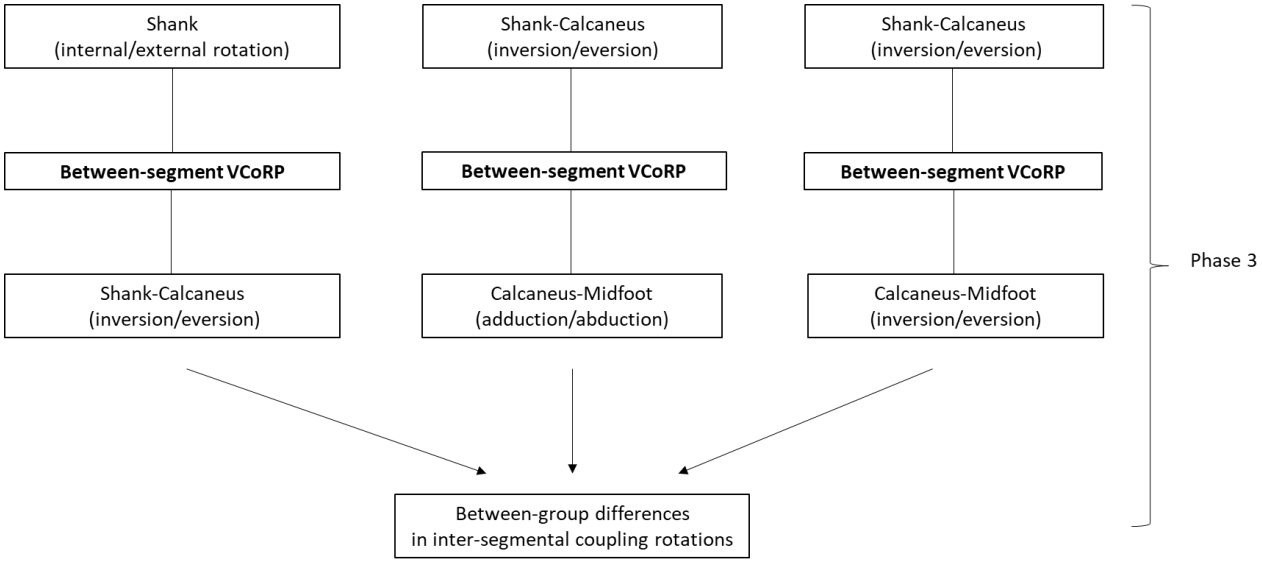

Table 6.1: Mean Continuous Relative Phase (CoRP) and CoRP variability (VCoRP) over the stance phase of gait for early RA and control group participants.

Coupling Angle	*Control CoRP*	*Early RA CoRP*	*Control VCoRP*	*Early RA VCoRP*	*p-vaue*
Shank Int/Ext - Rearfoot Inv/Ev	3.31	1.04	9.09	**8.86**	**0.00**
Rearfoot Inv/Ev - Midfoot Inv/Ev	-7.76	-7.58	5.16	**6.02**	**0.01**
Rearfoot Inv/Ev - Midfoot Abd/Add	-3.76	-2.25	3.34	**3.02**	**0.02**

6.5.1 Shank (internal/external rotation) – Shank-Calcaneus (inversion/eversion)

From figure 6.2, it can be seen that at heel strike (0%) the CoRP for the control group was in-phase. This indicates that both the shank and shank-calcaneus segments were rotating in the same direction. Between heel strike and 20% of stance, the CoRP was largely out-of-phase and negatively displaced, indicating that distal segment, or shank-calcaneus, rotated to a greater

magnitude than the shank. Between 20% - 30% of stance, coupling between the two segments interchanged between phase states, after which coupling became positively displaced until 57% of stance, where it became negative prior to toe-off.

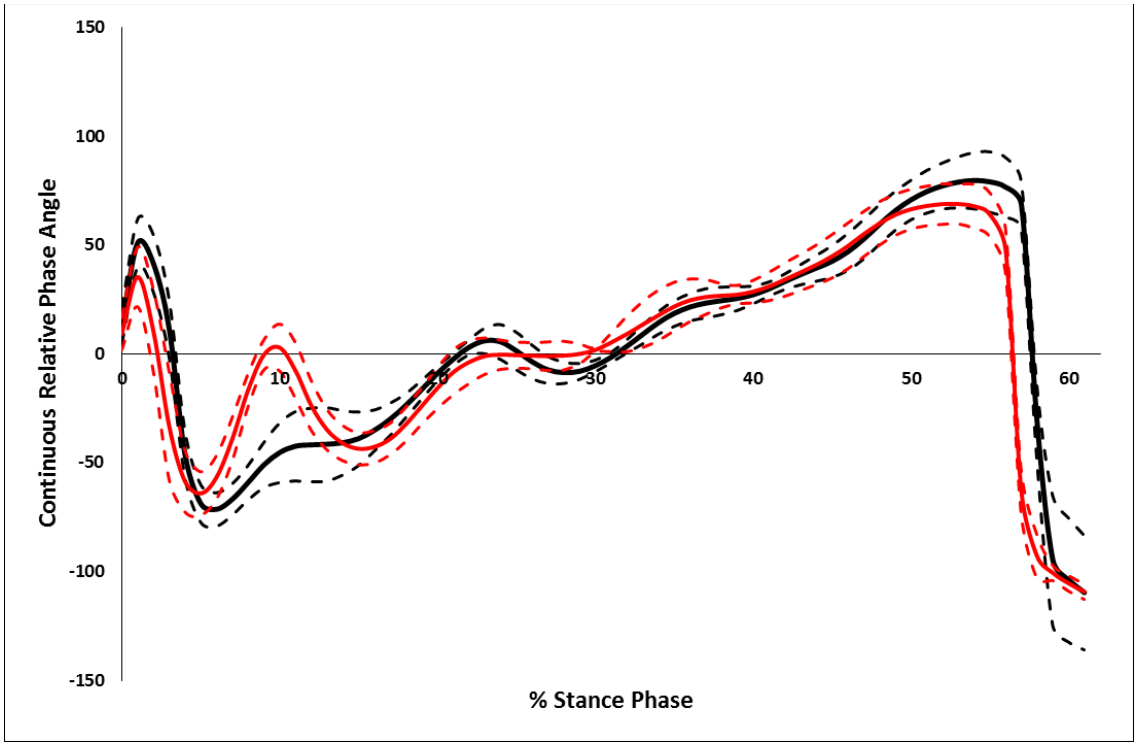

Figure 6.2: Continuous Relative Phase (CoRP) patterns between internal /external rotation of the shank-inversion/eversion of the calcaneus during stance. The Early RA CoRP pattern is represented in red. The control CoRP pattern is represented in black. The thick line indicates the CoRP with the thinner, broken line, represents the VCoRP.

Although visually, a very similar CoRP waveform was exhibited by the early RA group, differences were apparent in the period between 5-15%% of stance where this group exhibited a greater magnitude of negative CoRP. This indicates that in early RA participants, the shank-calcaneus segment rotated to a greater magnitude compared to the shank and for a longer duration.

The mean CoRP value for the control group was greater than that seen in the early RA group (Control, 3.31 ± 9.09, Early RA, 1.04 ± 8.86), indicating that a greater magnitude of inter-segmental rotation occurred between the shank and shank-calcaneus in these participants. Significant between-group differences were seen in CoRP variability which was reduced in the early RA group.

6.5.2 Shank- Calcaneus (inversion/eversion) – Calcaneus-Midfoot (inversion/eversion)

From figure 6.3, it can be seen that at heel strike, the CoRP of control group participants was in-phase, indicating that both segments rotated in the same direction. However, for the majority of the stance phase the CoRP remained out of phase. Between 0 – 25% the CoRP was largely positive, indicating that the rearfoot rotated to a greater magnitude than the calcaneus-midfoot (mean and SD). Between 15-22% the CoRP was relatively in-phase, after which it became out of phase and largely in a negative direction, indicating that the midfoot rotated to a greater magnitude than the rearfoot. By toe-off, the CoRP was again positively displaced.

The CoRP for the early RA group was similar. However, between 4-15%, the early RA participants exhibited a positive displacement of the CoRP, indicating that in these participants, the rearfoot rotated further compared to the midfoot. For both groups the mean CoRP was negative indicating that on average the midfoot moved to a greater magnitude compared to the rearfoot. The mean CoRP of the control group was greater however (Control, -7.76, early RA -7.58) and negatively displaced. However, a significant increase in VCoRP variability was seen in the early RA group. Whilst the coupling that occurred between these two segments was reduced in the early RA participants, the movement that occurred was more variable.

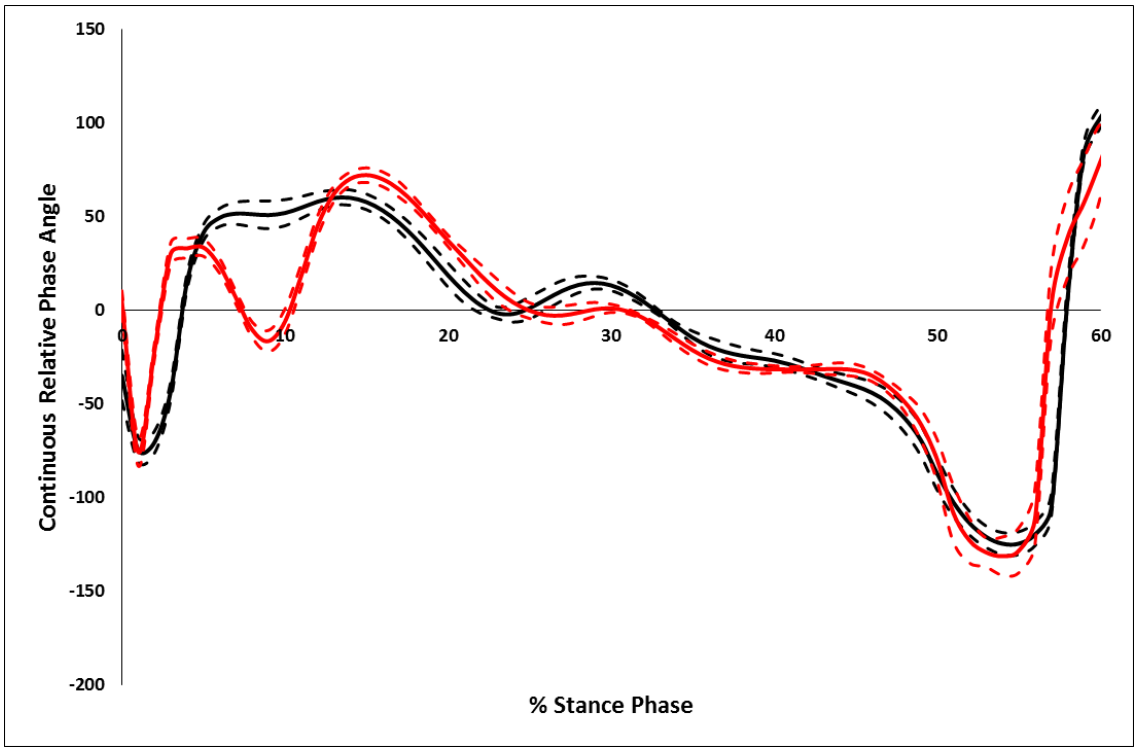

Figure 6.3: Continuous Relative Phase (CoRP) patterns between inversion/eversion of the calcaneus - inversion/eversion of the midfoot during stance. The Early RA CoRP pattern is represented in red. The control CoRP pattern is represented in black. The thick line indicates the CoRP with the thinner, broken line, represents the VCoRP.

6.5.3 Shank-Calcaneus (inversion/eversion) – Calcaneus-Midfoot (abduction/adduction)

From figure 6.4, it can be seen that at heel strike the CoRP was out of phase and negatively displaced, indicating that a greater magnitude of calcaneus-midfoot rotation relative to the shank-calcaneus was occurring. For the whole of the stance phase the CoRP was out of phase except for a period between 25-30% where it was relatively in-phase. Between 24-96% of stance the CoRP was negative, indicating that the midfoot motion exceeded that of the rearfoot. By toe-off, the CoRP had returned to a positive value.

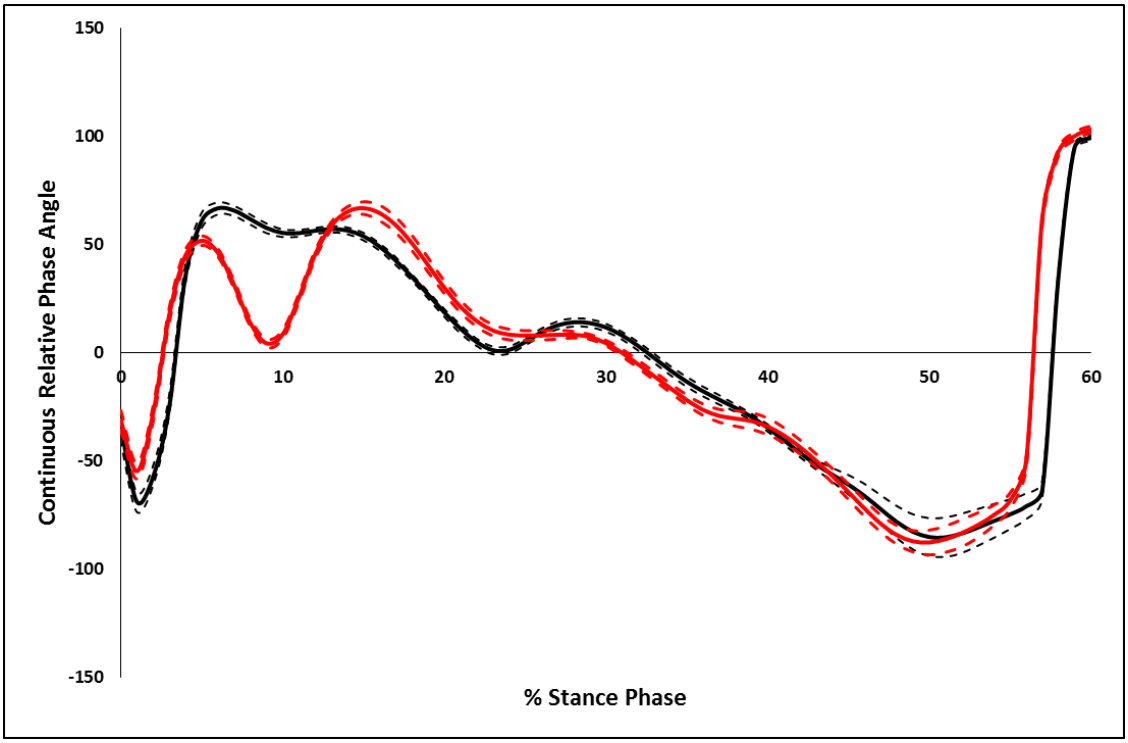

Figure 6.4: Continuous Relative Phase (CoRP) patterns between inversion/eversion of the shank - abduction/adduction of the midfoot during stance. The Early RA CoRP pattern is represented in red. The control CoRP pattern is represented in black. The thick line indicates the CoRP with the thinner, broken line, represents the VCoRP.

The CoRP for the early RA group was similar except for a longer duration of positive displacement of the CoRP between 10-23% indicating that in these participants the shank-calcaneus rotated to a greater magnitude compared to the calcaneus-midfoot. The mean CoRP value of both groups were negative indicating a greater magnitude of midfoot motion relative to the rearfoot. However, significant differences between groups in the variability of the CoRP show that in the early RA group, while less inter-segmental motion occurred, it was also accompanied by a reduction in the VCoRP or intrinsic variability.

6.6 Discussion

A dynamical systems approach was used in phase 3 of this study to investigate the presence of non-deterministic behaviour patterns in foot kinematics, ascertaining whether the variability of inter-segmental coupling relationships in participants with early RA is significantly different to those of healthy controls. To the best of the authors' knowledge, study 3 is the first to investigate the variability of kinematic coupling relationships within the foot in participants with early RA. The following sections discuss the findings of these analyses.

6.6.1 Intersegmental coupling involving the rearfoot and lower leg

From the data presented in phase 3 of this study, it can be seen that the mean CoRP coupling angle between transverse plane rotations of the lower leg and frontal plane rotations of the shank-calcaneus was reduced in early RA participants. The positive value of the mean CoRP reported in table 6.1 indicates that the proximal segment, i.e. the lower leg, underwent a greater magnitude of inter-segmental rotation compared to that of the shank-calcaneus. Importantly, the significant reduction in the VCoRP reported in this study may represent a previously unrecognised cause of mechanically based trauma in early RA, consistent with the concept of physiological complexity outlined in chapter 2 (section 2.3.4),

The significantly low variability of the VCoRP observed in early RA participants may be a reflection of the between-group differences in shank-calcaneus eversion patterns reported in early RA participants in chapter 5 (sections 5.9.7 and 5.10.5). In adopting a sustained increase in the magnitude of eversion that was observed at this segment, it is plausible that a decrease in the variability of intersegmental coupling patterns reflected a reduction in the available

degrees of freedom of movement at this segment in early RA participant. A reduction in the available degrees of freedom may explain why, on visual inspection, the CoRP representing rotations between the lower leg and the shank-calcaneus was observed to be altered in the first 15% of stance, corresponding to that period at early weight acceptance where subtalar joint pronation is thought to dissipate GRF during gait (Lui et al., 2012).

Reducing the degrees of freedom within which the shank-calcaneus operates would render this segment biomechanically less able to adapt to perturbations in its function during gait, placing both the joint and its associated ligaments and peritendinous structures under greater mechanical stress. This is an important consideration as synovitis at the subtalar joint is a frequent presentation of RA in the rearfoot, particularly at the sinus tarsi where it may lead to progressive weakening of the cervical, interosseous talocalcaneal and superomedial calcaneonavicular ligaments (Matsumoto et al., 2014). These ligaments provide resistance to eversion at the subtalar joint and their mechanical failure may in part explain why a displacement and change in the orientation of the talus is seen relative to the calcaneus and tarsal bones (Woodburn et al., 2010).

This interpretation is consistent with current consensus that individuals who demonstrate less variability in lower limb movement patterns are more susceptible to secondary pathologies (McClay and Manal, 1997; Miller et al., 2000; Heiderscheit et al., 2002; Peter et al., 2003; Seay et al., 2006; Pohl et al., 2006; Dierks et al., 2007; Chang et al., 2008; Hein et al., 2012; Lamb and Stocki, 2014). In the context of early RA, this is an important consideration, particularly where long term outcomes in early RA are concerned. Involvement of the rearfoot has been shown to affect between 30% - 60% of patients with long term disease (Matsumoto et al.,

2014). This is typically associated with the long term development of pes planus (Woodburn et al., 2004). It is plausible that the findings of this study, that repeated mechanical stresses secondary to a reduction in the VCoRP may constitute a source of microtrauma that may be responsible for the pathogenesis of long term functional outcomes in RA (Miller et a., 2008).

The findings of this study may also suggest that whilst these intersegmental rotations were repeatable, they occurred within a narrower kinematic range, reflecting fear-avoidance of activities resulting in pain and associated with increased physical deconditioning, decreased strength and muscular endurance. Cognitive responses are thought to bring about an avoidance of activity which in turn exacerbates functional impairment (Keefe et al., 2002). Indeed, Woodburn and Helliwell speculated that the presence of inflammatory disease, patterns of muscular activity, perhaps through modified pain avoidance gait, may simultaneously bring about atypical plantar pressure patterns reported in established disease along with irreversible long term structural rearfoot deformity (Woodburn and Helliwell, 1996). It is therefore plausible that the coordination of segments seen in early RA participants in the present study was such that there could be little deviation in the relative actions of these segments to produce relatively pain free gait. By contrast, the control group exhibited coupling actions which indicate that multiple combinations of coupling patterns could be utilised. This would be an optimal solution and one which serves to minimise trauma to these sites (Van Emmerick et al., 2014).

6.6.2 Intersegmental coupling involving the rearfoot and midfoot

Significant reductions in the VCoRP for this intersegmental coupling between the fontal plane rotations of the shank-calcaneus and transverse plane rotations of the calcaneus-midfoot were found in early RA participants. This indicates that these intersegmental rotations demonstrated a loss of coordinative flexibility. Similarly, the mean CoRP between frontal plane rotations between the shank-calcaneus and calcaneus-midfoot segments were reduced in early RA participants. The negative value of the CoRP indicated that the rotation of the distal segment, i.e. calcaneus-midfoot was greater than that of the shank-calcaneus.

In contrast, when frontal plane rotations between the shank-calcaneus and calcaneus-midfoot segments were investigated, the VCoRP was found to be significantly greater in the early RA group. This finding is consistent with an increase in the variability of coupling between these segments in early RA which may represent a loss of intersegmental coupling control in these participants. This would be consistent with the adoption of new coordination patterns in early RA that allow pain free movement. The findings of this study suggest that this results in an increase in stance variability between the subtalar joint and midtarsal joint, most probably as a consequence of an increased magnitude of subtalar joint pronation reported in chapter 5. It is also plausible that the midtarsal joint may be susceptible to such alterations in its function as a consequence of diffuse inflammation associated with early RA at both the talonavicular joint and sinus tarsi combined with the simultaneous involvement of plantarcalcaneonavicular ligament (Woodburn et al., 2002).

A loss of the structural integrity provided by this ligament results in a change in the direction and orientation of the bones of the midfoot. Lui et al., (2006) observed that such a loss of structural integrity increases plantarflexion at the talus which is accompanied by a simultaneous displacement of the calcaneus in a dorsolateral lateral and valgus rotation as pronation of the subtalar joint increases. The talus, cuboid and calcaneus have also be shown to jointly rotate in the direction of eversion (Woodburn et al., 2002). This would be consistent with the findings of chapter 5 which reported between-group differences in the magnitude, timing and duration of both rearfoot and midfoot kinematics in early RA, reporting a greater magnitude of eversion and abduction at these segments. The reduction in walking speed observed in the early RA participants may also have contributed to a reduction in the contraction of the surrounding musculature. Combined with the smaller range of motion at the rearfoot and midfoot segments, this may have decreased the tensile strain upon proximal ligaments (Woodburn et al., 2002). The combined effect of reduced stiffness of both muscles and ligaments may have resulted in more flexible coupling relationships being created.

6.7 Limitations of study

Whilst the rationale for using a dynamical systems approach to the study of musculoskeletal pathology in early RA was given in chapter 2 (section 2.3.13) and chapter 6 (section 6.1), the analysis of intersegmental coupling is still an emerging area of research. Ambiguity concerning the contribution of the CoRP to musculoskeletal pathology remains a feature of its use, arising primarily from the way in which these data are normalised and interpreted (Kurz and Stergiou., 2002). This section discusses these considerations with respect to phase 2 of study 2.

Normalisation: When analysing the CoRP, it is assumed that kinematic data are sinusoidal in nature (Lamb and Stöcki., 2014). This may not necessarily be true for all data in every gait cycle, particularly when considering the possibility that physiological complexity in early RA may be associated with underlying disease mechanisms that potentially modify kinematics to produce non-linear behaviour patterns. The presence of non-linearity in kinematic data becomes important when processing these data prior to analysis. Normalising angular velocity data produces scalar multiples of the original segment trajectories. Consequently, differences in amplitude between segments do not affect the coupling measures (Kurz and Stergiou, 2002). The method of normalisation described by Hamill et al., (1999) used in study 2 does not distinguish between the form that a kinematic waveform takes. Though Perter et al., (2003) argue that where waveform data are sinusoidal, the precise method of normalisation is irrelevant, where data are non-sinusoidal, normalisation may modify the CoRP curve both graphically and mathematically. This results in frequency artefacts which may either increase or decrease the amplitude of the CoRP waveform depending which method of normalisation is used (Lamb and Stöcki, 2014). As normalisation techniques may fundamental alter the shape and amplitude of the CoRP, it is possible that they may influence the manner in which the CoRP is interpreted.

Interpretation: As the CoRP is in essence a function of the position and angular velocity of one segment relative to another, it has been argued that describing its contribution to the pathogenesis of musculoskeletal pathology is both difficult and subjective (DeLeo.et al., 2004). This arises from differences in the manner by which the temporal dispersion of the CoRP may be interpreted. Perter et al., (2003) have previously argued that CoRP values approaching 180° do not necessarily indicate that opposing segments are rotating in opposite directions. By contrast, the present research followed current consensus which still maintains this to be the

case (Miller et al., 2008). To mitigate against these limitations, the CoRP was not analysed in isolation in study 2. Rather, significant between-group comparisons were made using its variance component, the VCoRP. It is acknowledged, however, that additional investigation is required in a larger group of early RA participants in order to further clarify the role of altered intersegmental coupling as an on-going injury mechanism in early RA.

6.8 Conclusion

In this study, 3D motion capture found evidence of significant between-group differences in non-deterministic behaviour patterns in foot kinematics which may act as a contributory source of mechanically based trauma in early RA. That these data are not detectable using conventional forms of kinematic analysis is an important finding, suggesting that alterations in inter-segmental coupling should also be investigated when screening for mechanical foot pathology in participants with early RA within the first twelve months following diagnosis.

To explain the presence of altered segmental foot kinematics reported in early RA participants in study 2, linear regression analysis is used in study 3 to test the fourth and fifth hypotheses of this thesis. The next chapter investigates the relationships between altered segmental kinematics in early RA and measures of disease activity, disease impact and rheumatology physical function.

Chapter 7: Explanatory Variables of Segmental Foot Kinematics in Adults with Early RA

In study 2, participants with early RA were found to exhibit altered foot kinematics at the shank, rearfoot, midfoot and first MPJ. The relationship between altered foot kinematics in early RA and measures of disease activity, disease impact and rheumatology physical function was investigated in study 3. The results of study 3 are reported in this chapter.

7.1 Introduction

In the absence of validated outcome measures for use in the musculoskeletal assessment of the lower limb in patients with early RA, chapter 2 (sections 2.4.1 to 2.4.18) highlighted the surrogate role that composite measures of disease activity and patient-reported assessment of disease impact have played in the clinical evaluation of musculoskeletal pathology in early RA. This is reflected in the conceptual framework of this thesis. Within this framework, a relationship exists between measures of early RA disease activity, disease impact and rheumatology physical function and the assessment of musculoskeletal impairment using 3D motion capture. However, these relationships have yet to be investigated.

In study 2, PCA identified significant between-group differences in the mode of variance of 3D kinematic data. Specifically, these were located at the shank-calcaneus, calcaneus-midfoot and first MPJ. In moving forward, we believe this may be the first study designed to investigate the relationship between these findings with measures of early RA disease activity and patient-

reported assessments of disease impact using linear regression analysis. To the best of the authors knowledge, there are no published data investigating these relationships in early RA.

7.2 Aims

The aim of study 3 was to determine the explanatory relationships between segmental foot kinematics in early RA measures of disease activity, disease impact and rheumatology physical function.

Data from this study was used to answer the second and third research questions of this thesis:

- Is there an association between the biomechanical function of the foot and lower limb in early RA with measures of rheumatology physical function?

- Is there an association between the biomechanical function of the foot and lower limb in early RA with measures of disease activity?

7.3 Hypotheses

Data from study 3 was used to test the following hypotheses:

- (H_4) - Relationships will be found between lower limb biomechanical function in early RA and measures of disease activity

- (H_5) - Relationships will be found between lower limb biomechanical function in early RA and measures of physical impairment

7.4 Study design

Linear regression analysis was used to investigate relationships between the kinematics of the shank, rearfoot, midfoot and first MPJ in early RA and measures of disease activity, disease impact and rheumatology physical function. To determine which independent variables significantly explained segmental foot kinematics in early RA, linear regression was undertaken in two phases. These are illustrated in figure 7.1.

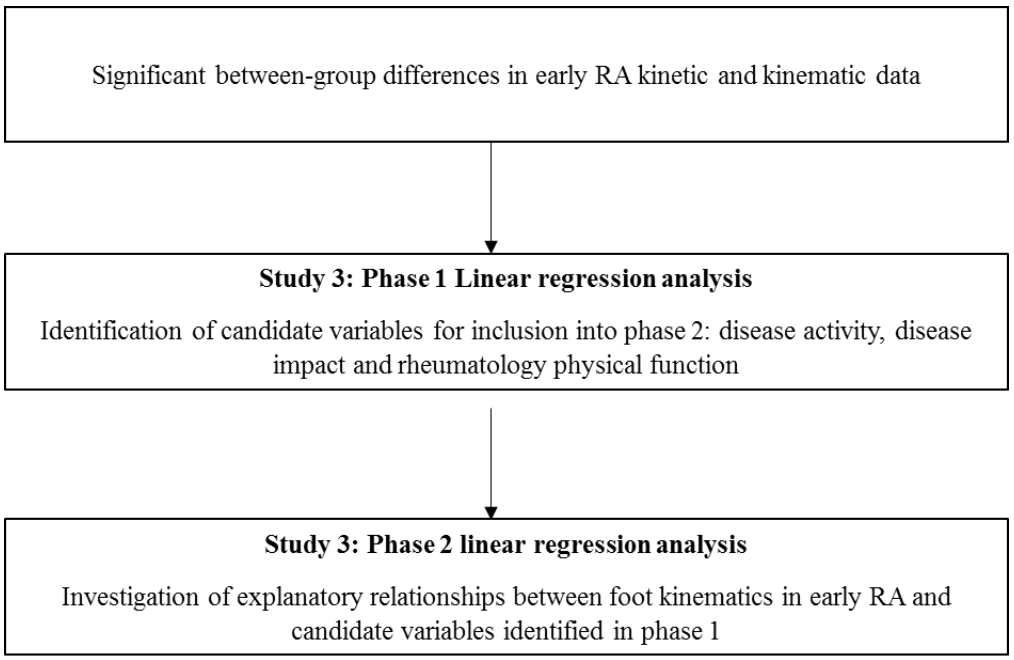

Figure 7.1: Flow diagram of study 3

7.5 Data Analysis

To investigate hypotheses the fourth and fifth hypotheses of this thesis, study 3 was undertaken in two phases. In both phases, linear regression analysis was used to investigate explanatory relationships between early RA segmental kinematics and measures of disease activity, disease

impact and rheumatology physical function. Linear regression analysis is described in chapter 3 (section 3.9.12).

7.6 Phase 1: Linear regression analysis

The following sections describe the study design of phase 1. The results of this phase are then presented.

7.6.1 Participants

Associations between rheumatology physical function, disease impact and disease activity with walking velocity were explored in a group of 32 early RA participants (mean age 45.34 ± 10.22 years, male/female ratio 9:23). To assess group differences in these parameters an age and gender match control group of 31 healthy participants was also recruited (mean age 41.87 ± 10.74 years, male/female ratio 9:22). Participant anthropometric data are presented in table 7.1. Data on disease activity and disease impact for early RA participants is presented in table 7.2.

Table 7. 1: Mean ± S D early RA (N= 32) and Control Group (N = 31) Anthropometric Data

Parameter	*Units*	*Early RA Group Mean*	*Control Group Mean*	*p-value*
Age	Years	45.34 ± 10.22	41.42 ± 10.04	0.08
Male: Female Gender	Total	8:24	10:20	
Height	M	149.61 ± 30.84	**165.55 ± 8.04**	**0.01**
Weight	Kg	93.94 ± 39.53	**72.15 ± 15.65**	**0.00**
Time Since Diagnosis	Months	10.14 ± 7.41	N/A	

Table 7. 2: Mean ± SD early RA Group (N=32) Disease Activity Parameters

Parameter	*Mean*
HAQ	0.84 ± 0.95
VAS (mm)	40.21 ± 31.82
LFIS 1	10.85 ± 4.75
LFIS 2	11.54 ± 9.01
DAS28	3.84 ± 1.22
DAS-CRP	3.76 ± 1.26
CRP (mg/l)	10.54 ± 11.74
ACPA positivity	0.55 ± 0.50
ACPA Value	13.17 ± 14.85
ESR (mm/hr)	17.77 ± 11.34

7.6.2 Dependent variable

The value of a regression coefficient depends upon the independent variables that are entered into a regression model and care should be taken when determining which explanatory variables to use. This decision should be based upon the results of previous research and the substantive theoretical importance of each variable (Field, 2009). Spatial-temporal data were collected on all participants at self-selected walking speed. Walking speed was significantly reduced in the early RA participants recruited for this study compared to their controls (early RA, 1.10 ± 0.17, Controls 1.10 ± 0.09). In the main group of early RA participants (n = 32), walking speed was the primary variable used to evaluate gait which was common to all participants regardless of whether they had elected to attend for subsequent 3D motion capture. Alterations in walking speed have been reported to modify the segmental kinematics of the foot in able-bodied participants (Dubbledam et al., 2010). Walking speed has also been shown to be a contributory factor in in explaining modified foot kinematics in participants with established RA of 9 years (Dubbledam et al., 2011). For these rationale, walking speed was chosen as the dependent variable representing lower limb biomechanical function during gait.

7.6.3 Independent Variables

Chapter 2 reviewed the inter-relationship between disease activity, joint damage and physical impairment. From the literature review it is apparent that the severity of outcomes in RA are determined several factors. As disease activity, disease phenotype and initial HAQ score have all been associated either independently or as coexisting factors in determining the severity of outcomes in RA, the following variables were automatically selected for inclusion into the initial set of independent variables for multiple regression analyses: DAS28, DAS-CRP, CRP, RF, anti-citrullinated protein antibodies (ACPA) and HAQ.

7.6.4 Linear associations

To identify additional candidate independent variables, associations between walking speed and measures of disease activity, physical impairment, spatial-temporal parameters and foot posture were assessed using Pearson's correlation coefficients. This method was used to identify variables which may contribute to multicollinearity, by determining where covariance between related variables was present. Where linear associations between related variables and walking speed were identified, candidate variables were removed prior to performing regression analysis. The results of these analyses are presented in table 7.3.

The linear relationships between walking speed, measures of disease activity, physical impairment, disease Impact and spatial-temporal parameters show that walking speed in participants with early RA was associated with cadence, step length and the toe-off (%) (Table 7.3).

In participants with early RA, adaptations in walking speed were not associated with the length of time from diagnosis, FPI-6, mean grip strength, timed walking, timed button, TUG, VAS, LFIS1 or LFIS2.

The following independent variables were included as independent variables into regression models: time since diagnosis, FPI-6, mean grip, timed walk, timed button, TUG, VAS, LFIS1, LFIS2, DAS28, DAS-CRP, CRP, ESR, RF and HAQ.

Table 7.3: Linear association between walking speed in early RA Participants and measures of disease activity, physical impairment and spatial-temporal parameters

Parameter	*Walking Speed*
Time Diagnosis	-0.289
FPI6	0.089
Mean Grip	0.221
Timed Walk	0.28
Timed Button	-0.306
TUG	0.092
VAS	0.056
LFIS1	-0.481
LFIS2	-0.321

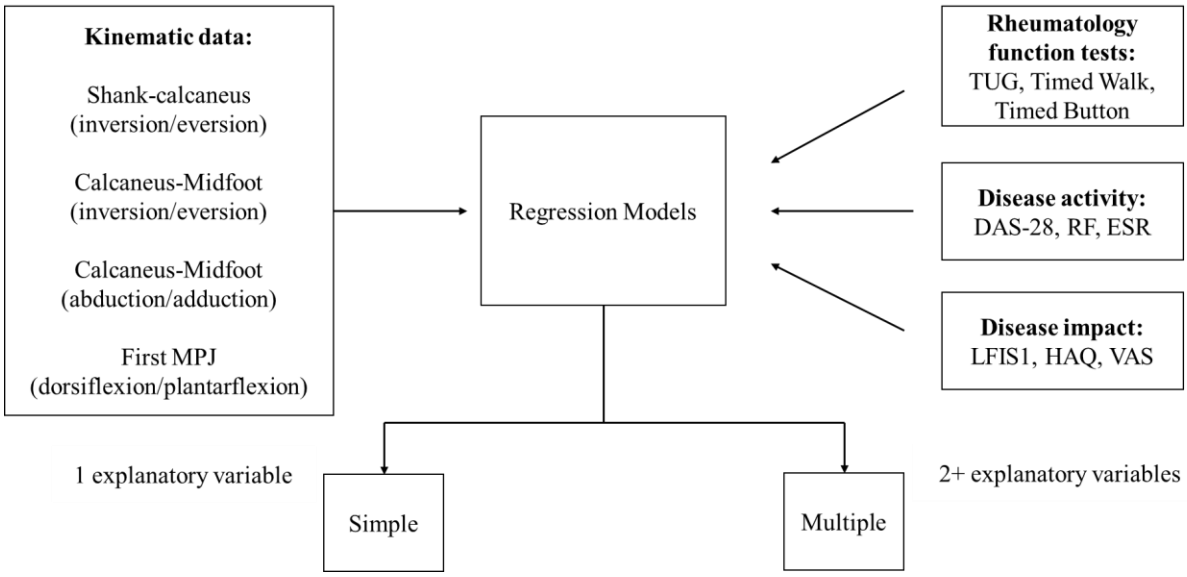

Figure 7.2: Independent variables included in linear regression model

7.6.5 Linear regression

Independent variables were grouped into the following categories: measures of disease activity, measures of disease impact, measures of rheumatology physical function, measures of foot posture and temporal-spatial measures. Separate regression analyses were carried out by entering data according to category using a stepwise method illustrated in figure 7.3.

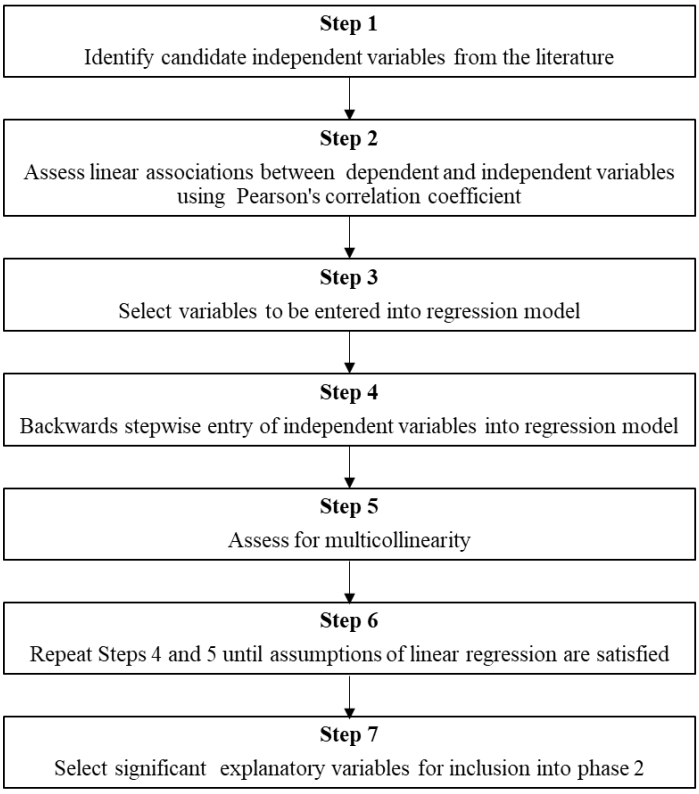

Figure 7.3: Flow diagram of regression analysis conducted in phase 1.

7.6.6 Results

The results of the linear regression analysis undertaken in phase 1 are presented in table 7.4.

Table 7.4: Significant explanatory variables of walking speed in participants with early RA

Dependent Variable	*Explanatory Variable*	*β*	*SE B*	*R2*	*P-value*
Walking Speed	ACPA	0.645	0.03	0.48	0.00
Walking Speed	RF	-0.338	0.03	0.48	0.00
Walking Speed	ESR	0.236	0.01	0.48	0.00
Walking Speed	LFIS1	-0.57	0.01	0.33	0.00
Walking Speed	Timed Button	-0.34	0.01	0.19	0.00
Walking Speed	Timed Walk	0.29	0.01	0.19	0.00
Walking Speed	FPI-6	0.26	0.01	0.07	0.01

7.6.7 Measures of disease activity

The following multiple regression model was used to analyse the association between walking speed, ACPA, the presence of RF and ESR:

$$\text{Walking Speed}i = bo + b_1\, ACPA\; i + b_2\, RF\; i + b_3\, ESR\; i + \varepsilon i$$

A significant regression equation was found (F(3,103), = 33.766, p = < .000), with an R^2 of 0.481. The predicted velocity of gait in participants with early RA was equal to 1.03 + - 0.003 (ESR) + -0.129 (RF) + 0.222 (ACPA), where ACPA was coded as 1 and 0, rheumatoid factor positivity was coded as 1 and 0 and ESR was measured in millimetres/hour. ACPA, RF and ESR were significant explanatory variables of walking speed.

7.6.8 Measures of physical impairment

The following single regression model was used to analyse the association between walking speed and the footwear/impairment dimension of the LFIS:

$$\text{Walking Speed}i = bo + b_1\, LFIS1\; i + \varepsilon i$$

A significant regression equation was found (F (1.068, 2.180), = 51.033, p = <0.000), with an R^2 of 0.329. The predicted velocity of gait in participants with early RA was equal to 1.31 + -0.02 (LFIS1), where the LFIS1 is measured on a scale between 0 and 21. The LFIS was a significant explanatory variable of early RA walking speed.

7.6.9 Measures of rheumatology physical function

The following multiple regression model was used to analyse the association between walking speed, timed button test and timed walking:

$$\text{Walking Speed}i = bo + b_1 Timed\ Button\ i + b_2\ TimedWalking\ i + \varepsilon i$$

A significant regression equation was found (F (0.640, 2.605), = 12.154, p = < 0.000), with an R^2 of 0.194. The predicted velocity of gait in participants with early RA was equal to 0.94 + - 0.00 (timed button) + -0.00 (timed walk), where timed button was measured in seconds and timed walk was measured in metres/second. Timed button and timed walk were significant explanatory variables of walking speed.

7.6.10 Measures of foot posture

The following single regression model was used to analyse the association between walking speed and the FPI-6:

$$\text{Walking Speed}i = bo + b_1\ FPI6\ i + \varepsilon i$$

A simple linear regression was calculated to explain early RA walking speed based on the FPI-6. A significant regression equation was found (F (0.224, 3.029), = 7.680, p = < 0.007), with an R^2 of 0.069. Early RA participants predicted gait velocity was equal to 1.06 + 0.017 (FPI-6) where the FPI-6 is measured on a scale between -10 and +12. The FPI-6 was a significant explanatory variable for walking speed.

7.6.11 Summary of phase 1 results

- A multiple linear regression model incorporating disease activity biomarkers showed that the presence of ACPA, rheumatoid factor, and ESR acted as explanatory variables of walking speed.

- A multiple linear regression model incorporating rheumatology physical function tests as outcome measures of performing a timed button and a timed walk test also acted as explanatory variables of walking speed.

- A simple linear regression model incorporating measures of disease impact showed that the footwear/ impairment dimension of the LFIS acted as explanatory variable of walking speed.

- A simple linear regression model incorporating measures of foot posture showed that the FPI-6 acted as explanatory variable of walking speed.

7.7 Phase 2 Linear regression analysis

The following sections describe the study design of phase 2. The results of this phase are then presented.

7.7.1 Participants

To determine explanatory relationships of altered foot kinematics in early, a second regression analysis was conducted using data taken from a subgroup of 18 early RA participants who had

attended 3D motion capture sessions. Participant demographics are presented in table 7.5. Data on disease activity, disease impact and rheumatology physical function are presented in tables 7.6.

Table 7.5: Mean ± SD of anthropometric data of groups evaluated for linear regression analysis in phase 2

Parameter	*Units*	*Early RA Group Mean*	*Control Group Mean*	*p-value*
Age	Years	45.50 ± 11.90	42.24 ± 7.82	0.37
Male: Female Gender	Total	5:13	7:10	0.13
Height	M	149.61 ± 30.84	**165.55 ± 8.04**	**0.03**
Weight	Kg	93.94 ± 39.53	**72.15 ± 15.65**	**0.02**
Time Since Diagnosis	Months	12.78 ± 10.33	NA	

Table 7.6: Mean ± SD of measures of disease activity and physical impairment in early RA participants (N = 18)

Parameter	*Early RA Mean*
HAQ	4.55 ± 16.37
VAS (mm)	29.17 ± 21.29
LFIS 1	7.76 ± 4.12
LFIS 2	5.76 ± 6.08
DAS28	3.17 ± 0.74
DAS-CRP	3.16 ± 1.02
CRP (mg/l)	6.47 ± 5.70
ACPA positivity	0.61 ± 0.49
ACPA Value	1.35 ± 0.75
ESR (mm/hr)	17.92 ± 15.73

Table 7.7: Mean ± SD of spatial-temporal and physical function data for early RA and control groups

Parameter	*Control Mean*	*Early RA Mean*	*p- value*
Walking Speed (m/s)	1.30 ± 0.09	**1.10 ± 0.17**	**0.00**
Cadence (step/min)	115.18 ± 8.51	116.02 ± 13.15	0.83
Step length (m)	13.43 ± 24.65	13.01 ± 27.83	0.96
Stride Length (m)	1.35 ± 0.06	1.24 ± 0.22	0.07
Step Time (s)	0.52 ± 0.04	0.52 ± 0.08	0.30
Stride Time (s)	1.04 ± 0.08	1.07 ± 0.13	0.41
Toe off (%)	59.72 ± 1.33	**61.09 ± 1.84**	**0.02**
FPI-6	3.65 ± 2.68	3.72 ± 3.57	0.72
Grip Strength (kg)	29.60 ± 6.13	24.46 ± 13.21	0.24
6 min Walk (m)	550.41 ± 63.76	**476.14 ± 87.10**	**0.01**
Timed Button (s)	44.93 ± 8.60	**67.03 ± 41.03**	**0.04**
TUG (s)	6.97 ± 1.26	8.68 ± 3.28	0.06

7.7.2 Dependent Variables

The kinematic parameters chosen as dependent variables for inclusion within the regression analysis were: shank-calcaneus frontal plane rotation, shank-calcaneus transverse plane rotation, calcaneus-midfoot frontal plane rotation, calcaneus-midfoot transverse plane rotation and first MPJ sagittal plane rotation. Each segmental rotation was then entered into a separate regression equation as a dependent variable.

7.7.3 Independent Variables

In phase 1, the following independent variables were shown to significantly explain walking speed: ACPA, RF, ESR, LFIS1, timed button test, timed walking and the FPI-6. To identify additional candidate independent variables, associations between segmental foot kinematics and measures of disease activity, physical impairment, spatial-temporal parameters and foot

posture were assessed using Pearson's correlation coefficients. The results of this analysis are presented in table 7.8.

Table 7.8: Pearson's correlations showing linear relationships between independent variables of disease activity and physical impairment and frontal plane angular rotations at the shank-calcaneus segment in participants with early RA.

Parameter	**Shank-Calcaneus (Inv/Ev)**	**Shank-Calcaneus (Abd/Add)**	**Calcaneus-Midfoot (Inv/Ev)**	**Calcaneus-Midfoot (Abd/Add)**
Walking Speed m/(s)	**0.67****	0.17	**0.67****	0.3
Cadence (step/min)	-.513*	-0.36	-0.51	-0.29
Step Length (m)	**.484***	0.12	**.484***	-0.11
Stride Length (m)	0.19	-0.08	0.19	0.24
Step Time (s)	0.11	0.1	0.11	-0.17
Stride Time (s)	**.475***	0.28	**.475***	-0.01
Toe-off (%)	**-.530***	0.01	**-.530***	-0.37
Time Since Diagnosis (yr)	-0.17	0.03	-0.17	**-.477***
RFPI6	0.01	0.13	0.01	0.13
Mean Grip (kg)	0.13	-0.32	0.13	0
Timed Walk (m)	0.27	0.39	0.27	**.513***
Timed Button (s)	-0.22	0.41	-0.22	-0.34
TUG	0.2	**.537***	0.20	**-.541***
VAS	0.16	-0.24	0.16	0.14
LFIS1	**-.598***	-0.29	**-.598***	-0.08
LFIS2	-0.26	-0.28	-0.26	0

*p=<0.05

7.7.4 Shank-calcaneus (inversion/eversion)

The linear relationships between frontal plane angular rotations of the shank-calcaneus inversion/eversion, disease activity, physical impairment, disease impact and spatial-temporal parameters show that walking speed in participants with early RA was associated with walking speed, cadence, step length, toe-off (%) and the first dimension of the LFIS (Table 7.8).

The increased magnitude of eversion of the shank-calcaneus segment in early RA participants was significantly associated with cadence ($rp = -.513$; $p < 0.01$) and step length ($rp = .484$; $p < 0.01$), toe-off (%) ($rp = -.530$; $p < 0.05$) and the FFIS ($rp = -.598$; $p < 0.05$) .

In participants with early RA, no adaptations in walking speed were associated with stride length, step time, time since diagnosis, FPI-6, mean grip, timed walk, timed button, TUG, VAS and LFIS2.

Significant associations between the dependent variable of frontal plane motion at the shank-calcaneus and the independent variables of cadence, step length, stride time and toe-off (%) were shown. To avoid multicollinearity these independent variables were not included in the regression analysis.

Independent variables entered into linear regression analyses were: stride length, step time, time since diagnosis, FPI-6, mean grip, timed walk, timed button, TUG, VAS, LFIS1, DAS28, DAS-CRP, CRP, ESR, RF and HAQ.

7.7.5 Shank-calcaneus (abduction/adduction)

The linear relationships between transverse plane angular rotations of the shank-calcaneus segment, disease activity, physical impairment, disease Impact and spatial-temporal parameters show that shank-calcaneus inversion/eversion in participants with early RA was associated with CRP (Table 7.8).

Increased abduction at the shank-calcaneus segment in early RA participants was significantly associated with ($rp = -528$; $p < 0.01$). In participants with early RA, no adaptations in shank-

calcaneus motion were associated with walking speed, cadence, step length, stride length, step time, step length, stride length, step time, time diagnosis, FPI-6, mean grip, timed walk, timed button, TUG, VAS, LFIS2 and HAQ.

Whilst significant associations were shown between the dependent variable of transverse plane motion at the shank-calcaneus and the independent variables of TUG and CRP, as neither variable measures the same dimension of interest, both were retained for regression analysis.

Independent variables entered into linear regression analyses were: walking speed, cadence, step length, stride length, step time, step length, stride length, step time, time diagnosis, FPI-6, mean grip, timed walk, timed button, TUG, VAS, LFIS1, DAS28, DAS-CRP, CRP, ESR and RF

7.7.7 Calcaneus-midfoot (inversion/eversion)

The linear relationships between frontal plane angular rotations of the shank-calcaneus inversion/eversion, disease activity, physical impairment, disease Impact and spatial-temporal parameters show that walking speed in participants with early RA was associated with walking speed, cadence, step length, toe-off (%) and the first dimension of the LFIS (Table 7.8).

The increased magnitude of eversion of the shank-calcaneus segment in early RA participants was significantly associated with cadence ($rp = -.513$; $p < 0.01$) and step length ($rp = .484$; $p < 0.01$), toe-off(%) ($rp = -.530$; $p < 0.05$) and the LFIS ($rp = -.598$; $p < 0.05$) .

In participants with early RA, no adaptations in walking speed were associated with stride length, step time, FPI-6, mean grip, timed walk, timed button, VAS, and LFIS2.

Significant associations between the dependent variable of frontal plane motion at the calcaneus-midfoot and the independent variables of walking speed, cadence, step length, stride time and toe-off (%) were shown. To avoid multicollinearity, of these, only walking speed was retained as an independent variable.

Independent variables entered into linear regression analyses were: walking speed, stride length, Step time, foot off, time diagnosis, FPI-6, mean grip, timed walk, timed button, TUG, VAS, LFIS2, DAS28, DAS-CRP, CRP, ESR, RF and HAQ.

7.7.8 Calcaneus-midfoot (adduction/abduction)

The linear relationships between transverse plane angular rotations of the calcaneus-midfoot segment, disease activity, physical impairment, disease Impact and spatial-temporal parameters show that walking speed in participants with early RA was associated with walking speed, cadence, step length, toe-off (%) and the first dimension of the LFIS (Table 7.8).

The increased magnitude of abduction of the shank-calcaneus segment in early RA participants was significantly associated with time since diagnosis ($rp = -.477$; $p < 0.01$) and TUG ($rp = -.541$; $p < 0.01$). In participants with early RA, no adaptations in walking speed were associated with walking speed, cadence, step length, stride length, step time, stride time, foot off, FPI-6, mean grip, timed walk, timed button, VAS and LFIS2.

Whilst significant associations were shown between the dependent variable of transverse plane motion at the calcaneus-midfoot and the independent variables of time since diagnosis and TUG, as neither variable measures the same dimension of interest, both were retained for regression analysis.

Independent variables entered into linear regression analyses were: walking speed, cadence, step length, stride length, step time, stride time, toe-off (%), time since diagnosis, FPI-6, mean grip, timed walk, timed button, TUG, VAS, LFIS2, DAS28, DAS-CRP, CRP, ESR, RF and HAQ.

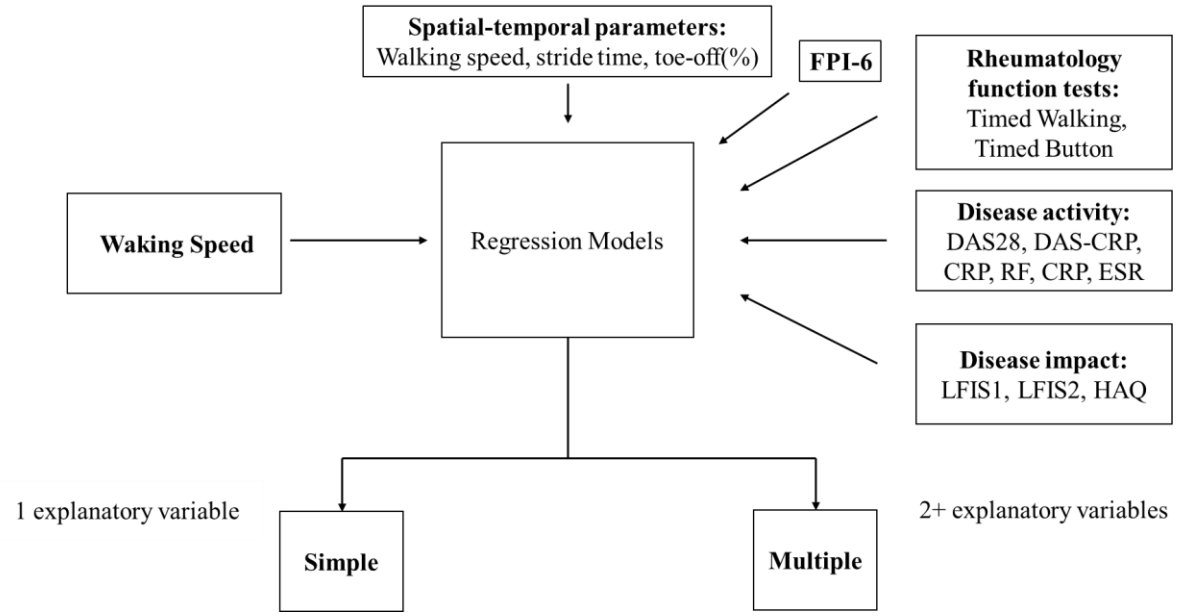

Figure 7.4: Independent variables entered into linear regression model in phase 2

7.7.9 Linear regression

Linear regression in phase 2 of this study was undertaken using a backwards stepwise method which is illustrated in figure 7.5.

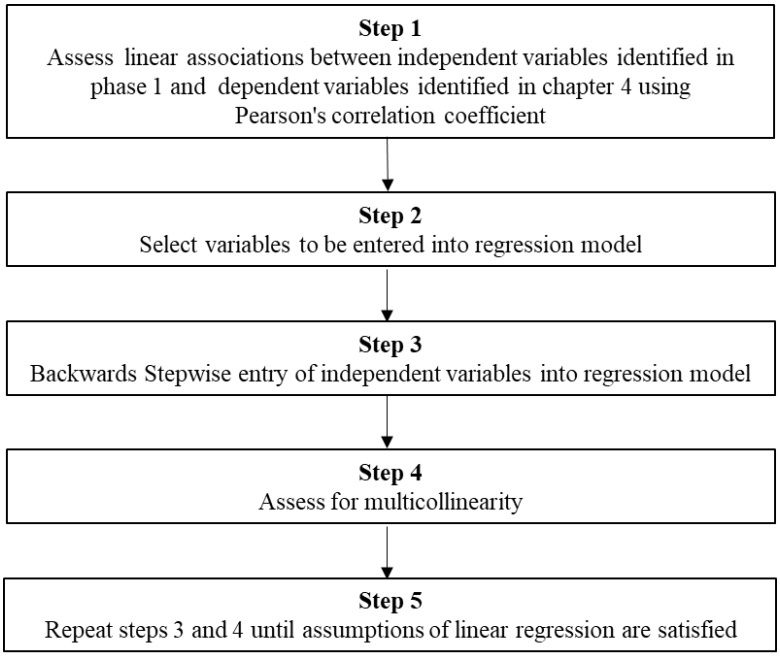

Figure 7.5: Flow Diagram of multiple regression analysis of variables as part of phase 2 of study 3

7.7.10 Results

Significant explanatory relationships of linear regression between segmental angular rotations of the foot and independent variables in participants with early RA are presented in table 7.9.

Table 7.9: Significant explanatory variables of segmental angular rotations in participants with early RA

Dependent Variable	*Explanatory Variable*	*β*	*SE B*	*R2*	*P-value*
Shank-Calcaneus: Frontal Plane PC1	Walking Speed	0.68	152.75	0.46	0.00
Shank-Calcaneus: Frontal Plane PC1	LFIS	-0.6	6.65	0.36	0.01
Shank-Calcaneus: Frontal Plane PC1	RF	-0.62	80.05		0.03
Calcaneus-Midfoot: Frontal Plane PC1	Toe-off (%)	-0.5	22.15	0.25	0.03
Calcaneus-Midfoot: Frontal Plane PC1	Walking Speed	0.48	236.92	2.25	0.04
Calcaneus-Midfoot: Frontal Plane PC1	Timed Walk	0.53	0.18	0.37	0.02
first MPJ: Sagittal Plane PC1	Step Length	-0.99	1.067	0.37	0.0

7.7.11 Explanatory variables of frontal plane angular rotations: shank-calcaneus

Walking Speed: The following single regression model was used to analyse the association between fontal plane motion at the shank-calcaneus and walking speed:

$$\text{Shank} - \text{Calcaneus (frontal plane motion)} i = bo + b_1 Walking\ Speed\ i + \varepsilon i$$

A significant regression equation was found (F (158803.5, 189279.9), = 12.585, p = < 0.003), with an R^2 of 0.456. Participants predicted gait velocity was equal to -978.92 + 541.90, where walking speed is measured in metres/second. Walking speed was a significant explanatory variable of frontal plane motion at the shank-calcaneus.

Measures of Disease Impact: The following single regression model was used to analyse the association between frontal plane motion at the shank-calcaneus and the first dimension of the LFIS:

$$\text{Shank} - \text{Calcaneus (frontal plane motion)} i = bo + b_1 LFIS\ 1\ i + \varepsilon i$$

A significant regression equation was found (F(107042.8, 29884.5.8), = 8.371, p = <0.011), with an R^2 of 0.358. Participants predicted principal component score for frontal plane kinematics of the shank-calcaneus segment was equal to -240.64 + -19.24 where the LFIS 1 is measured on a scale between 0 and 21.

Disease Activity: The following single regression model was used to analyse the association between frontal plane motion at the shank-calcaneus and the presence of RF:

$$Shank - Calcaneus\ (frontal\ plane\ motion)i = bo + b_1 RF\ i + \varepsilon i$$

A significant regression equation was found. Participants predicted principal component score for frontal plane kinematics of the shank-calcaneus segment was equal to -245.35 + -200.93, where RF positivity is coded as either 1 or 0.

7.7.12 Explanatory Variables of frontal plane angular rotations: calcaneus-midfoot

Toe-off (%): The following single regression models were used to analyse the association between frontal plane motion at the calcaneus–midfoot and the percentage of gait at which foot-off occurred:

$$\text{Calacneus} - \text{Midfoot (frontal plane motion)}i = bo + b^1\ Toe - off(\%)\ i + \varepsilon i$$

A significant regression equation was found (F (16198.5, 477727.2), = 5.425, p = < 0.33), with an R^2 of 0.253. Participants predicted principal component score was equal to 3137.83 + -51.59,

where foot-off is measured as a percentage of gait. Toe-off (%) was a significant explanatory variable for frontal plane kinematics for the calcaneus-midfoot segment.

Walking Speed: The following single regression models were used to analyse the association between frontal plane motion at the calcaneus–midfoot and walking speed:

$$\text{Calacneus} - \text{Midfoot (frontal plane motion)} i = bo + b_1 \, Walking \; Speed \; i + \varepsilon i$$

A significant regression equation was found (F (150255.7, 489448), = 4.912, p = < 0.042), with an R^2 of 0.235. Participants predicted principal component score for frontal plane kinematics of the calcaneus-midfoot segment was equal to - 592.87 + 525.09, where walking speed is measured in metres/second. Walking speed was a significant explanatory variable of frontal plane kinematics of the calcaneus – midfoot segment.

Timed walk: The following single regression models were used to analyse the association between frontal plane motion at the calcaneus–midfoot and the percentage of gait at which foot-off occurred:

$$\text{Calacneus} - \text{Midfoot (frontal plane motion)} i = bo + b^1 Toe - off(\%) \; i + \varepsilon i$$

A significant regression equation was found (F(36414.862, 56562.734), = 4.507, p = < 0.031), with an R^2 of 0.372. Participants predicted gait velocity was equal to - 17.60 + 0.45, where timed walk is measured in metres.

7.7.13 Explanatory variables of sagittal plane angular rotations: first MPJ

Step Length: The following single regression model was used to analyse the association between sagittal plane motion at the first MPJ and spatial-temporal parameters:

$$\text{First MPJ (dorsiflexion)}i = bo + b_1\, WalkingSpeed\ i + \varepsilon i$$

A significant regression equation was found (F (36414.862, 56562.734), = 4.507, p = < 0.031), with an R^2 of 0.372. Participants predicted gait velocity was equal to - 483.07 + -95.07 where step length is measured in centimetres.

7.7.14 Explanatory Variables of Transverse Plane Angular Motion: Shank-Calcaneus

No significant explanatory variables were identified for this parameter.

7.7.15 Explanatory variables of transverse plane angular rotations: calcaneus-midfoot

No significant explanatory variables were identified for this parameter.

7.7.16 Summary of Phase 2 results

- Simple linear regression models in which spatial-temporal parameters were incorporated showed that walking speed, step length and toe-off (%) acted independently as significant explanatory variables of frontal plane kinematics of the shank-calcaneus segment.

- A single linear regression model in which the footwear/impairment dimension of the LFIS was incorporated showed that it acted as a significant explanatory variable of frontal plane kinematics of the shank-calcaneus segment.

- A single linear regression model in which RF was incorporated showed that it acted as a significant explanatory variable of frontal plane kinematics of the shank-calcaneus segment.

- A single linear regression model in which the percentage of gait at which foot off occurred was incorporated showed that it acted as a significant explanatory variable of frontal plane kinematics of the calcaneus-midfoot segment.

- A single linear regression model in which walking speed was incorporated showed that it acted as a significant explanatory variable of frontal plane kinematics of the calcaneus-midfoot segment.

- A single linear regression model in which step length was incorporated showed that it acted as a significant explanatory variable of sagittal plane kinematics of the first MPJ.

- No significant explanatory variables were identified for transverse plane kinematics for both the shank-calcaneus and calcaneus-midfoot segments.

7.8 Discussion

Chapter 2 of this thesis highlighted the role that measures of disease activity, disease impact and rheumatology physical function may play in the absence of validated assessments of foot and lower limb musculoskeletal impairment in early RA. The results of study 3 suggest that the majority of these measures do not explain altered foot kinematics in early RA participants. It is believed that this is the first time that explanatory variables of altered segmental kinematics in early RA have been investigated. The following sections discuss these findings.

7.8.1 Explanatory variables of segmental foot kinematics in early RA

Of the measures of disease activity investigated, none were found to explain segmental foot kinematics in the early RA participants recruited to this study. Only the presence of the biomarker RF was found to have a significant relationship to segmental foot kinematics in early RA. The r^2 (R square) for this linear regression model was 0.358, indicating that significant associations for RF explained 36% of frontal plane motion of the shank-calcaneus. On the basis of these findings, the fourth hypothesis (H_4) stating that relationships will be found between lower limb biomechanical function in early RA and measures of disease activity, is rejected. The alternative hypothesis (H_0) is therefore accepted.

Furthermore, of the measures of disease impact and rheumatology physical function investigated, only the first dimension of the LFIS demonstrated a significant explanatory relationship to early RA foot kinematics. Specifically, the r^2 (R square) for this model was 0.358 indicated a significant association for LFIS1, accounting for 36% of the total variance in

frontal plane motion of the shank-calcaneus. With only the footwear/impairments dimension of the LFIS being found to explain frontal plane motion at the shank-calcaneus, it is difficult to conclude that the measures of disease impact and rheumatology physical function explain segmental kinematics in early RA. For this reason, on the basis of these findings, the fifth hypothesis (H_5) stating that relationships will be found between lower limb biomechanical function in early RA and measures of physical impairment, is rejected. The alternative hypothesis (H_0) is therefore accepted.

In contrast to these findings, of the spatial-temporal parameters investigated, three were observed to have a significant explanatory relationship to segmental kinematics of the shank-calcaneus and calcaneus-midfoot. Walking speed was found to be an explanatory variable of frontal plane angular rotations of the shank-calcaneus in early RA participants. Of the independent variables investigated, it exhibited the strongest relationship, exhibiting an r^2 (R square) for this model of 0.456 indicating that walking speed accounted for 46% of the variance in these segmental kinematics. For segmental kinematics at the calcaneus-midfoot, relationships to spatial-temporal parameters were weaker but were nonetheless found to be significant with an The r^2 (R square) for this model of 0.235. Walking speed was therefore observed to explain 24% of the total variance in frontal plane motion of the calcaneus-midfoot. Similarly, toe-off (%) exhibited an r^2 (R square) for this model of 0.253 indicating that associations with toe-off (%) explained 26% of the variance in frontal plane motion at this segment. Finally, step length exhibited an r^2 (R square) of 0.372 for this model, therefore explaining 37% of the variance in sagittal plane motion at the first MPJ.

Spatial-temporal parameters are known to be affected in early disease. Reductions in self-selected speed in early RA participants have been reported to range between 0.90m/s to 0.96m/s (Khazzam et al., 2007; Turner et al., 2008). Reductions in walking speed have therefore been viewed as a primary explanatory factor underpinning pain avoidance strategies in the presence of active disease (Van der Leeden., 2008). Chapter 5 (section 5.11.2) raised this as a plausible explanation underlying the observation that the significant reductions in walking speed and delayed termination of stance observed in early RA participants, may have facilitated the significant between-group differences in segmental foot kinematics reported in study 2. Though the biomechanical model segments analysed in study 2 incorporated joint sites within the foot where the pathology of early RA is known to occur (Matsumoto et al., 2014), the findings of study 3 suggest that in early RA, the disease process itself may not necessarily demonstrate a direct influence in modifying foot kinematics. Rather, alterations in segmental foot kinematics may be modulated indirectly through alterations in spatial-temporal parameters.

7.8.2 Disassociation between dependent an independent variables

The disassociation observed in this study between measures of disease activity, disease impact and rheumatology physical function may have arisen from several factors. These encompass issues of the internal validity, sensitivity and specificity of these measures. The following section discusses these aspects.

Measures of physical impairment: Whilst an explanatory relationship between segmental foot kinematics in early RA participants and the first dimension of the LFIS, none was found for

the HAQ. In explaining this finding, it should be acknowledged that treatment paradigms in the management of early RA have changed radically since the original development of the HAQ in 1978. At its inception, the sensitivity and specificity of the HAQ were originally established to predict levels of physical impairment in participants presenting with chronic disease from the Stanford Outcome in Rheumatoid Arthritis (ORA) study (Fries et al., 1982). By contrast, levels of self-reported disability seen in the present study are similar to reports from larger modern RA cohort studies where an incidence of milder disease has been reported (Sokka., 2005) . Lower levels of self-reported physical impairment have been reported in several modern cohort studies which coincide with a general trend towards a more favourable course of disease activity and more aggressive therapy. Coupled with a shift in the clinical presentation of early RA since the HAQ was first introduced, the insufficient sensitivity of the HAQ to changes in foot kinematics may explain why explanatory relationships were not found.

The lack of explanatory capacity of the HAQ may also have arisen from the fact that, as a measure of functional impairment, it is likely to be insufficiently specified for its application to the present group of early RA participants where altered joint kinematics were the dimension of interest. The internal and external validity of the HAQ is based upon operational definitions of physical function that markedly differ from that of altered joint kinematics which may be attributable to the original development of the tool. Whilst an excellent correlation for the category of 'walking' of 0.88 was reported by Fries et al., (1982) in the original validation of the HAQ, to the authors' knowledge, it yet to be validated against a single continuous measure of 3D kinematics.

The HAQ was also conceived as a multidimensional assessment of functional impairment conceptualising physical impairment as an outcome measured within a patient-centric value system. With functional capacity being measured across nine general component categories, only with a single category of 'gait outdoors' assesses lower limb function. When scoring the HAQ, to capture the multidimensional nature of physical function, the highest score from each category is taken and summed with the rest. This results in a final HAQ score that provides an overall measure of physical function rather than focusing upon walking ability alone. Therefore, the operational definition of global physical function used during the development of the HAQ is quite different to that of localised foot kinematics. Furthermore, 3D motion capture is an objective measure of musculoskeletal function (McGinley et al., 2013). By contrast, the HAQ is a subjective self-reported assessment of function across multiple dimensions and therefore may be influenced by the subjective 'internal standards' or expectations of the participant concerning their physical health and wellbeing (Maska et al., 2011).

Measures of disease activity: In study 3, no measure of disease activity acted as an explanatory variable of segmental foot kinematics in early RA participants. This is an important finding with particular reference to the DAS28. Historically, the interaction between disease activity in early RA with measures of radiological damage and physical impairment has been viewed as part of a central paradigm explaining long term outcomes. One explanation for these findings is that the omission of the joints of the foot and ankle in the DAS28 means that active disease within the foot may be missed. As a possible limitation of the DAS28, this was highlighted in chapter 2.

In addition, it plausible that the criterion validity of the patient-reported 28-joint count incorporated into the DAS28 may not be a true reflection of the clinical state of the disease Though the DAS28 was originally developed from data on 227 patients recruited from hospital outpatient clinics (Prevoo et al., 1995), operational definitions of physical function have never been applied to the DAS28; it was developed primarily as a composite measure of disease activity only. The DAS28 was primarily designed to discriminate between high and low disease activity, not functional impairment.

The criterion validity may also be an issue. This stems from the original validation of the DAS28. Physical disability was assessed using the HAQ. Radiographically detected damage in the hands and feet were used in the original development and validation of the DAS28 by Prevoo et al., (1995). To assess criterion validity, correlations between individual DAS28 scores and physical impairment measured using the HAQ were analysed. Pearson's correlations between the DAS28 and HAQ were reported to be weak (0.38 ± 0.039). By comparison, linear associations between the DAS28 and radiographic damage were found to be stronger, ranging from 0.50 (number of erosions); 0.52 (joint space narrowing) and 0.53 (total erosions and narrowing). Since its original validation, disease activity has subsequently been shown to be independently and longitudinally associated with radiographic damage. Therefore, in terms of criterion validity, whilst the DAS28 appears to give a true measure of clinical status, this is only where radiological damage is taken into account. This is not so where lower limb walking patterns are concerned.

7.8.5 Biomarkers used in diagnosis

Rheumatoid factor was the only biomarker of disease that was found to act as an explanatory variable of altered foot kinematics in early RA participants. In this study, 72% of the participants exhibited sero-positive disease, mirroring the incidence reported by Humphreys et al., (2012). From a clinical perspective the utility the presence of RF as an explanatory variable may be limited. As a biomarker of disease, RF is not exclusive to the incidence of rheumatoid arthritis. Furthermore, it may also be present in healthy individuals as they age. The sensitivity of RF is around 50-70%. Although higher titres of RF increase its specificity in the presence of inflammatory arthritis, a limitation of using RF as a biomarker is that titres do not reliably change with disease activity. Whilst patients are more likely to develop erosive disease than in seronegative disease. Their primary value is as a prognostic indicator of erosions (Schellekens et al., 2000).

Neither the ESR, ACPA nor anti-CCP were found to act as explanatory variables of foot kinematics in early RA. Levels of all the biomarkers reported in the present study were low-to-moderate. Whilst these biomarkers are included in ACR/EULAR Core set variables, they are not outcome measures but are instead process measures, representing the intermediate products of the disease classification process. The use of process indicators to assess an outcome such as physical impairment assumes that they relate directly to that outcome; this is frequently not the case (Berwick and Knapp, 1987).

The ESR is used primarily as an indirect method of measuring elevations in the concentrations of acute phase plasma proteins. It is non-specific to RA and may be present in a number of

pathophysiological states where inflammation is present. Accordingly, the CRP is an acute phase reactant which is elevated in the presence of inflammation, generally reflecting the extent of tissue injury. Like the ESR, elevated levels of CRP are seen in other inflammatory conditions other than RA. Although included in ACR/EULAR classification criteria for RA, the ESR and CRP have little use as specific tests in the diagnosis of RA. Rather, they are used to follow disease activity and monitor response to treatment.

Whilst the management of joint inflammation is usually accompanied by a decrease in the ESR and CRP, by themselves, they are not sufficient to determine treatment response as progression in joint damage may be seen where improvement in acute phase reactant are present (Schellekens et al., 2000). For this reason, the ESR and CRP are not used alone when determining disease activity. Anti-CCP is used as a surrogate indicator of radiological damage/progression. Similar to RF, its presence at early diagnosis predicts more radiographic progression and a strong association between anti-CCP and the development of erosions has been demonstrated (Schellekens et al., 2000, Salvador et al., 2003). Anti-CCP titres do not however reliably change with disease activity. Therefore, like RF, anti-CCP can help identify patients more prone to severe disease (Schellekens et al., 2000).

7.9 Limitations of the study

It may be argued that the significant correlations reported in phase 2 of study 3 between early RA foot kinematics, disease activity and disease impact may not necessarily indicate causation. Rather, these relationships may instead be indicative of a correlation between variables under the influence of a common, albeit unidentified cause (Kumer-Ainur., 2007). In moving forward

with this research, the reproducibility of these findings becomes an important factor in confirming the relationship between measures of disease activity, disease impact and physical function with alterations in early RA kinematics. The results of this study may be difficult to replicate for several reasons. These centre on issues concerning recruitment, correlation between variables and the presence of error in data.

Participant recruitment: The level of recruitment for this research fell short of sample size calculations (chapter 3, section 3.5). Though linear regression has previously been used to investigate explanatory variables of foot kinematics using similar sample sizes (Altman and Davis, 2012; Muhaffey et al., 2016; Caravaggi et al., 2016), it has been argued that to ensure the stability of regression estimates, the number of participants should exceed the number of independent variables by a factor of ten (Field, 2009). It is therefore possible that the small sample size of the study resulted in regression estimates reported in study 2 that were overinflated.

Correlation between variables: A second consideration is the extent to which kinematic data followed deterministic behaviour patterns as described in chapter 2 (section 2.3.13). When conduction linear regression, successive measurements of the dependent variable should be unrelated. The value of the dependent variable should also be random (Field, 2009). As consecutive kinematic data occur within a time series taking place across the duration of the gait cycle, it is possible that autocorrelation may have occurred between successive data points (Kamer-Ainur., 2007). Converting these data into principal component scores prior to linear regression as described in chapter 3 (section 3.8.10) may have mitigated against this by reducing these data to single values. Whether the standard error associated with each regression

coefficient was understated as a result remains a possibility. This is an important consideration as narrower prediction and confidence intervals that would occur would mean that the multiple correlations reported in this study may have been overstated in value (Yoo et al., 2014). Similarly, despite tests for multicollinearity, correlation between the independent variables entered into the regression models in phases 1 and 2 may still have been present. This would be of particular relevance to the use of walking speed, timed walking and TUG. Whilst care was taken not to enter these variables simultaneously into either the single or multiple regression models for phases 1 and 2, an eventual overestimate of the regression coefficient R^2 of the effect of these variables upon foot kinematics in phase 2 cannot be used out (Yoo et al., 2014).

Error: Lastly, the ability to reject the null hypothesis may have been influenced by the fact that simple linear regression assumes a lack of error within each measured variable (Field, 2009). Though an acceptable level of repeatability was demonstrated for 3D motion capture data in study 1, error may still be presumed to be a feature of these data, albeit within clinically acceptable levels. This may also be considered true of all other measures used within these analyses. For this reason we cannot assume that errors associated with the regression models used in study 3 and those of all other independent variables were independent of one another. Though the multiple regression models used in study 3 should have mitigated against this by entering multiple variables in a step-wise manner (Field, 2009), further investigation is required to confirm these results.

7.10 Conclusion

The results of study 3 suggest that current measures of disease activity, disease impact and rheumatology physical function do not act as explanatory variables of altered foot kinematics in early RA participants. Rather, altered foot kinematics appear to be explained largely as a result of early RA participants adopting significant reductions in walking speed which were accompanied by a delay in the termination of stance.

It is acknowledged that there were limitations to this study which arose from difficulties in recruitment, the possible correlation between variables and the presence of error in data. However, these results suggest that measures of disease activity, disease impact and rheumatology physical function do not act as surrogates of mechanically based foot pathology detectable using 3D motion capture. From a clinical perspective, this strengthens the case for the use of 3D motion capture in the early detection and management of musculoskeletal impairment in early RA.

Chapter 8: Summary of Thesis

The principal aims of this thesis were to investigate the presence of altered biomechanical function in early RA participants and to investigate relationships between these and measures of disease activity, disease impact and rheumatology function. Chapter eight draws together the results of this thesis and discusses their clinical implications. The limitations of this thesis are highlighted and discussed along with proposals for further research.

8.1 Lower limb biomechanical function in early RA

This thesis has reported that within the twelve months of diagnosis of RA, despite low-to-moderate levels of disease, significant alterations in spatial-temporal parameters and foot kinematics were detectable using 3D motion capture. For this reason the hypothesis (H_1) stated in chapter 1 (section 1.3) that 'Lower limb spatial-temporal parameters in adults with early RA will be different from those of age and gender matched adults' can be accepted. Likewise, the hypothesis (H_3) that 'lower limb joint kinematics in adults with early RA will be different from those of age and gender matched adults' can also be accepted. By contrast, in the absence of detectable between-group differences in lower limb kinetics, the hypothesis (H_2) that 'lower limb joint kinetics in adults with early RA will be different from those of age and gender matched adults' can be rejected. The alternative hypothesis (H_o) that 'lower limb joint kinetics in adults with early RA are not different from those of age and gender matched adults' can therefore be accepted.

8.2 Early assessment of residual foot pathology in RA

The results of this thesis demonstrate that a determination towards significant mechanical foot pathology may be established early in the natural history of the disease. In extending the work of previous studies, data from this thesis indicate that such alterations are likely to go undetected using current NICE guidelines on the assessment of RA (NICE, 2009). This has fundamental clinical implications when considering the early pathogenesis of lower limb physical impairment. In translating the laboratory based findings of this thesis into clinical practice, several recommendations are made which are contextualised on this basis. These aim to mitigate against the long term functional consequences of those altered spatial-temporal and segmental kinematics reported in chapters 5 and 6. These recommendations are based upon the principals of early detection and intervention.

On the principal of early detection, based upon these findings the first recommendation is that all early RA patients be referred for an assessment of mechanically based foot pathology as soon as possible following diagnosis. This recommendation is based upon current consensus that in order to positively influence the trajectory of early physical impairment, the management of residual foot pathology should be undertaken as soon as possible (Woodburn et al., 2010). This recommendation aligns to current standards of care published by PCR and ARMA that advise that patients should be referred for foot examination within three months of diagnosis by practitioners integrated into the multidisciplinary team (ARMA, 2004; PCR, 2011).

The need to make this recommendation is also based upon low levels of referral to specialist foot health services; only 42% of patients requiring foot health management are currently referred to specialist services by their rheumatology consultant (Hendry et al., 2013). A key explanatory factor that this thesis has already highlighted is the use of DAS28 driven assessment of disease activity which excludes an examination of the foot. With persistent synovitis being reported within the feet in the presence of DAS28 defined remission (Landewe et al., 2006; Van der Leeden et al., 2010; Wechalekar et al., 2012), consultations based primarily upon this composite measure are likely to underestimate the impact of residual foot pathology in early disease (Williams, 2015).

This is not the only factor that must be addressed if the early detection of mechanically based foot pathology in RA is to be improved. In making this recommendation it is acknowledged that there are fundamental limitations concerning the education and training of rheumatology specialists that may also need to be addressed. De Souza et al., (2016) noted that only 62% of rheumatology clinicians felt competent in foot examination. Historically, not all clinicians report receiving effective training (Woodburn and Helliwell, 1997; Helliwell, 2003) and a lack of medical undergraduate training in the UK on foot examination remains a key factor influencing the frequency of foot examinations. Whilst up to 80% of consultant, 75% of registrars and 67% of rheumatology nurses have been reported to have received postgraduate training, the nature of this training remains unspecified (De Souza et al., 2016).

8.3 The role of 3D motion capture in early RA

Outcome measures proposed by Woodburn et al., (2010) for the assessment of the foot in early RA advocate the use of the LFIS in preference to the direct measurement of function itself; clinical data on gait analysis were viewed by this group not as a primary outcome but instead as an extended outcome within the domain of 'function'. With biomechanical impairment of the foot viewed as a *red flag* presentation of the disease, this is counterintuitive but may be in response to the limited availability of validated biomechanical assessment tools. In resolving this paradox there is a need to incorporate an outcome measure that directly quantifies mechanical foot pathology which is both valid and reliable (Pynsent, 2001). Seen from this perspective there is a fundamental need to re-evaluate the manner by which mechanical foot pathologies in early RA are assessed.

Historically, musculoskeletal pathologies of the foot have been classified based upon clinical observation of structural pathologies and their assumed symptomology during gait. The classification of foot morphology and its association with mechanical dysfunction during gait are a central paradigm that still underpin the clinical examination of the foot. By far the most widely used paradigm of foot classification still practised by podiatrists is that proposed by Root and colleagues (Root et al., 1977). That the theoretical basis of this paradigm is being increasingly doubted should be of concern.

The common practice of assessing foot morphology using the static neutral positioning of the subtalar joint fails to sufficiently replicate those internal forces generated by muscle contraction that enable weight bearing kinematics to be replicated (Jarvis et al., 2012). For this reason,

static measures of foot abnormal morphology have also been found to poorly correlate to the magnitude or direction of segmental kinematics within the foot during gait. In the largest study to date examining the relationship between foot morphology and gait kinematics, the external validity of the Root paradigm was questioned by Jarvis et al., (2017). In a study of 140 asymptomatic participants using a 6 segment foot model described by Nester et al., (2014), this group found no relationship between abnormal foot morphology described by Root and colleagues and foot kinematics during gait.

A consensus that clinical experience is sufficient to discern normal from abnormal musculoskeletal function is a characteristic of current clinical practice (Jarvis et al., 2012). Using a modified Delphi technique, Jarvis and colleagues found that owing to the burdens of time, podiatrists choose to estimate and classify mechanically based disorders rather than ascertain these through direct measurement. Such an approach directly undermines measurement based interventions such as the prescription of functional foot orthoses. Yet Jarvis et al., (2012) found that traditional measurements of foot biomechanics exhibit very low inter-assessor reliability, with ICC values ranging between 0.61 (measurement of ankle range of motion) to 0.02 (measurement of limb length).

Current practices in podiatric biomechanics are therefore characterised by a level of theoretical uncertainty that does not necessarily represent a sound basis upon which the clinical examination of the foot should be undertaken. Adopting objective measures of musculoskeletal pathology which demonstrate an acceptable level of validity and reliability, even at the expense of time, would provide a more robust basis upon which clinical assessments would take place. To overcome current conceptual uncertainties, based upon the presupposition of unlimited time

and resources we recommend that 3D motion capture should be incorporated into current recommendations as an objective, validated and reliable assessment tool of gait analysis in early RA. It is also recommended that baseline 3D motion capture data be collected as soon as possible following diagnosis in all patients with a view to the long term monitoring of biomechanical function of the foot within the first two years of disease.

8.4 Early Intervention

Alterations in rearfoot and midfoot kinematics described in this thesis are similar to those observed in established disease (Woodburn et al., 2003). Without intervention, a decoupling of motion between these sites may occur within ten years of diagnosis which is associated with significant structural pathology (Woodburn et al., 2003). Woodburn and colleagues observed that by controlling altered rearfoot kinematics using functional orthoses, a normalisation of frontal plane motion at the rearfoot is achievable (Woodburn et al., 2008). Mechanically based interventions may therefore arrest the pathogenesis of long term physical impairment.

Despite fundamental limitations used in the assessment of musculoskeletal foot pathologies in early RA, the net effect of mechanically based interventions such as the prescription of functional foot orthoses has been reported to produce positive outcomes (Hawke et al., 2008). The reasons behind this may however centre upon the redirection of internal forces and abnormal tissue stress rather than through the reestablishment of any perceived structural normalcy (Zammit and Payne, 2007).

Because 3D motion capture is not theoretically embedded within current paradigms of podiatric biomechanics, as a clinical measure it would allow a greater emphasis to be placed upon explaining the mechanical basis of foot biomechanics during weight bearing that relate to the pathology and symptomology of early RA rather than through the assessment of foot morphology. Such an approach allows clinical interventions to be personalised to the needs of individual patients with orthotic prescriptions targeted in a manner that modifies tissue pathologies in specific structures rather than attaining a predefined magnitude of structural normalcy. Evidence supporting this approach was presented by Gibson et al., (2014), confirming that the prescription of functionally optimised orthoses to participants within the first two years of disease enhances subtalar and midtarsal joint kinematics, significantly reducing peak rearfoot eversion and navicular height. For this reason we recommend the use of 3D motion capture in the early targeted interventions of mechanical pathology in RA. In making this recommendation it is anticipated that this is an area of practice that may be delivered primarily by extended scope podiatrists in alignment with guidelines by Woodburn et al., (2010).

8.5 Relationships between altered foot kinematics in early RA and measures of disease activity

As a caveat to the recommendations made within this chapter, it should be recognised that there are time and cost implications that may prohibit the use of 3D motion capture within both the hospital and community care settings. The need to mitigate against the limitations of DAS28 driven assessment mean that alternative outcome measures that are predictive of altered foot kinematics in early RA should be available to practitioners. In addressing this, relationships

between lower limb biomechanical function and measures of disease activity, disease impact and rheumatology function were investigated in this thesis using linear regression analysis.

Regression analysis found that the increased magnitude of frontal plane angular rotations at the rearfoot were explained by the presence of RF, walking speed, the percentage of gait at which toe-off occurred and the footwear/impairment domain of the LFIS. The increased magnitude of frontal plane motion of the midfoot joint occurred independently of disease activity but was explained by the percentage of gait at which toe-off occurred, walking speed and the timed walk test. The only explanatory variable found relative to reduced first MPJ dorsiflexion was step length. The increased magnitude of abduction seen at the rearfoot and midfoot joint occurred independently of all variables entered into the regression model. Whilst these relationships were significant, the R^2 values for individual variables were weak. For these reasons, the hypothesis (H_4) stated in chapter 1 (section 1.3) that 'relationships will be found between lower limb biomechanical function in early RA and measures of disease activity' cannot be accepted. This is also true of the hypothesis (H_5) stated in chapter 7 (section 1.3) that 'relationships will be found between lower limb biomechanical function in early RA and measures of physical impairment' can be accepted.

In translating these findings to clinical practice it would be premature to make detailed recommendations for the adoption of specific outcome measures. However, the findings of this thesis do indicate that the incorporation of spatial-temporal parameters into current rheumatology core outcomes may be an area for further investigation. Such measures may provide a simple, cost effective clinical metric accessible to all members of the rheumatology multidisciplinary team. To translate the findings of this thesis into clinical practice this

recommendation is however predicated upon further research to confirm the findings of this thesis via a definitive trial. This is an area for further investigation that is recommended in order to extend upon the present research.

8.6 Access to 3D motion capture

As a final point of interest, whilst the recommendations made within this chapter have so far contextualised '*why*' and 'when' 3D motion capture should be used, they do not address how current levels of clinical demand may be met. This is an important issue of service access. As demand for healthcare is likely to grow, given current levels of service delivery it is unlikely that podiatrists alone will be able to meet predicted healthcare demands (Hendry et al., 2013). In addressing this, there is an implication as to '*who'* uses 3D motion capture. The findings of the present study strengthen the case for the deployment of extended scope podiatrists within the rheumatology multidisciplinary team in the early assessment, monitoring and management of residual foot pathology in RA in alignment with current recommendations (Woodburn et al., 2010). Furthermore, in the identification and control of inflammatory joint disease and mechanically based impairments this thesis acknowledges that podiatrists may fulfil a key role by routinely screening all patients with RA for mechanically driven pathologies within the first year of disease.

A limiting factor to this recommendation is that the access and provision of dedicated foot care services has historically been reported to be variable and service provision poor when compared to the foot health care needs of early RA patients (Brand et al., 2009; Rome et al., 2010; Royal College of Physicians, 2011). The need for foot health provision in the early RA

population has remained constant in the face of insufficient numbers of specialist practitioners (Redmond et al., 2006; Kings Fund, 2009; National Audit Office, 2009). Indeed, numbers of specialist podiatrists are unlikely to increase in the NHS (PCR, 2011). Therefore, to meet current and future demands, the cross-discipline use of 3D motion capture may be required when recommending that all early RA patients be assessed for mechanically based foot pathology.

8.7 Study limitations

There are a number of potential limitations to the studies undertaken within this thesis. These have been grouped below according to the following themes:

- Recruitment
- Sample size
- Bias
- Study design

8.7.1 Recruitment

An inherent limitation of cross-sectional analysis highlighted by Shekelle et al., (1999) is that the strength of evidence that is presented is consistent with that of non-experimental descriptive research. In contrast to randomised controlled trials which represent the highest categorisation of evidence and study based recommendations (grade 1A, A), cross sectional studies present evidence of a fundamentally lower magnitude (grade III, C). In addition, there a several

limitations to the present study which threaten the external validity of the evidence presented. Of these, the question arising over the generalisability of the study findings may be considered a central limitation. First among these threats is the issue of sample size. The small sample size of the study arose from difficulties in securing study sites, changes to the study design and recruiting sufficient numbers of early RA participants.

At the time of the original R&D submission in December 2012, recruitment sites had not been confirmed. Following submission of Site Specific Information Forms (SSI), R&D approval for the first study site (Homerton Hospital) was granted in July 2013 and recruitment at this site began in September 2013. Gaining R&D approval at Whipps Cross Hospital took longer than anticipated owing to administrative delays at this site. In addition, Barts Health required an internal peer review and financial impact assessment of the research. The Chief Investigator was also required to submit an Enhanced Disclosure and Barring Service (DBS) check and undertake Research Governance Framework (RGF) and Good Research Practice (GRP) training. R&D approval at this site was finally granted in 22/1/14.

An annual monitoring review in early 2013 proposed that the study be amended to confine recruitment of early RA participants to the first six weeks following diagnosis followed by a second study visit at twelve weeks. A substantial amendment to this effect was submitted to NRes Committee London- Bloomsbury on 8/10/13. A letter of favorable opinion was received on 18/10/13. Between July 2013 and September 2014, recruitment at Homerton University Hospital was slow due to a fall in the number of referrals of early RA cases reported by the onsite collaborator. Recruitment at the second site, Whipps Cross Hospital, was also slower than anticipated. A review of the recruitment strategy was undertaken in January 2015. It was

identified that following the amendment to the study design many prospective participants had been reluctant to participate within the first six weeks following diagnosis owing to the burdens of time and the adverse psychological impact of being newly diagnosed with RA.

The present study also faced competition for early RA participants at Homerton University Hospital from a Medical Research Council (MRC) funded study called TACERA (Towards a Cure for Early Rheumatoid Arthritis). To ameliorate against these factors it was decided to embed this study into recruitment sites allowing the Chief Investigator to meet prospective participants face-to-face at the point of referral and collecting data on physical function and disease impact with the option of a second study visit at the University of East London (UEL) Stratford campus for 3D gait analysis. To amend the data collection protocol, an application to apply for a research passport via the National Institute for Health Research (NIHR) was submitted in February 2015. Permission to access NHS Trust property was granted in the same month (Appendix 3). Data collection at both recruitment sites commenced from March 2015 onwards.

A continued level of low recruitment prompted a second review of the recruitment strategy which was undertaken in May 2015. It was agreed that, in addition to the factors previously highlighted, the restriction of participants to the first six weeks following diagnosis had had a significant negative impact on recruitment. To address this it was decided to return to the original inclusion criteria of studying early RA participants within the first two years following diagnosis as stated in the original grant application and REC documentation. It was anticipated that this would allow for a larger cohort of prospective participants from which to be recruited whilst increasing the number of out-patient clinical sessions that could be accessed. Both

recruitment sites were made aware of the revised recruitment strategy which commenced from June 2015 onwards until December 2016

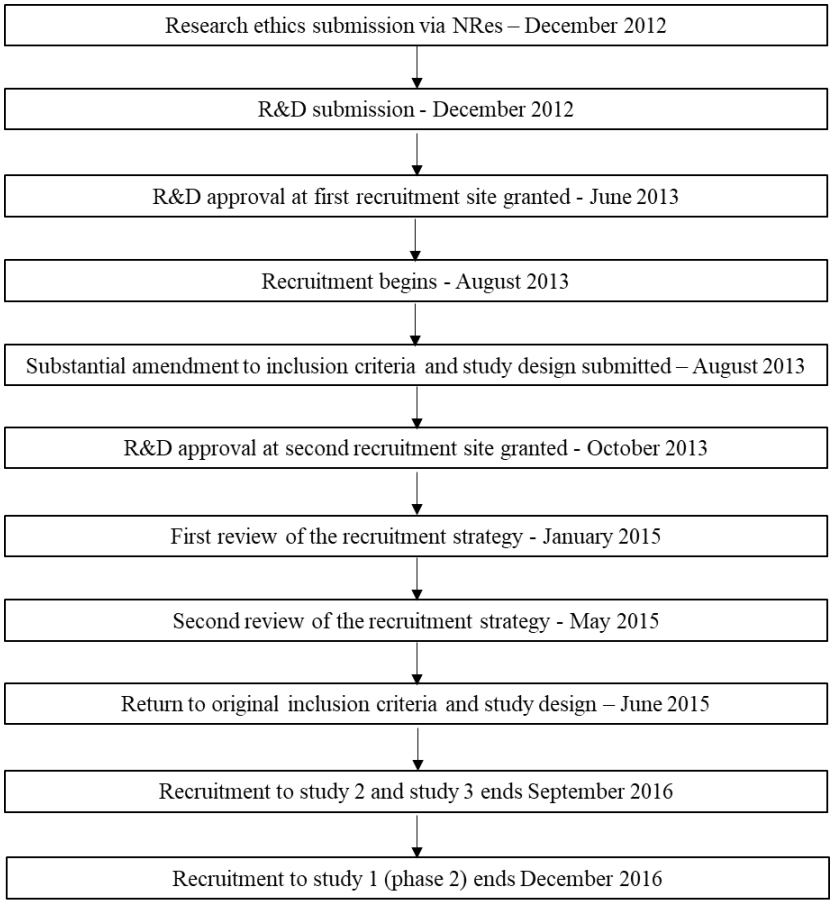

Figure 8.1: Flow diagram of participant recruitment

8.7.2 Sample size

A priori analysis of the sample size required for this study incorporating an alpha (α) level of significance of 0.05 and beta (β) level of error of 20% (80% power) was calculated to range between 61 to 773 participants depending upon the joint site studied. Difficulties in recruitment limited the sample size of the early RA group to eighteen participants. In terms of the statistical construct validity, this compromised the ability of the study to reject the null hypothesis. The

increased likelihood of type II error may explain why, despite an increase in the magnitude of flexion and accompanying joint moments exhibited at the hip and knee during gait by RA participants, between-group differences failed to reach statistical significance. It is plausible that significant group differences may have emerged given a larger study group.

8.7.3 Bias

In addition to the small sample size there is the possibility that the collective attributes of the early RA group were influenced by the recruitment process. To avoid selection bias participants were recruited from consecutive outpatient clinics. It is possible that self-selection bias occurred, altering the characteristics of the group with only the most willing participants exhibiting milder disease presentations volunteering to take part. It is of note that the early RA group was relatively homogenous group in terms of disease presentation and disease impact. Whilst such homogeneity may have limited the effects of inter-subject variation upon the dependent variable, whether the group's collective attributes can be generalised is questioned. These attributes may also have been affected in not controlling for factors such as weight, height and gait velocity, random systemic or non-systemic events that may affected the dependent variable. Furthermore, in the absence of a randomisation process it is possible that the composite characteristics of subjects may not have been distributed equally between groups as a function of chance alone.

An additional factor modulating how these characteristics were expressed was in the data collection process itself. The schedule for data collection was intensive. The presence of fatigue may have changed participant's responses to testing. By incorporating both motion capture and

rheumatology physical function testing. It may be argued that the act of collecting data may have altered participant responses to measurement, for example by stimulating change rather than recording passive behaviour.

8.7.4 Study design

Whilst there was evidence of an explanatory relationship between dependent and independent variables, the internal validly of the study could have been more robust. Whilst cross-sectional analysis is consistent with exploratory research, the inherent disadvantage of this approach is that it is likely that the dependent variable i.e. lower limb biomechanical function may be altered in these participants by the passage of time under the influence of disease activity. It had been the intension to recruit participants at an earlier stage within the natural history of the disease. *Very early RA* has been identified as that stage within the disease inhabiting the first six weeks following diagnosis. Following the progress of disease during the first two years rather than conducting a cross sectional study would have enabled the emergence and characterisation of between-group differences to be made in a manner never previously undertaken. In studying data longitudinally, relationships between lower limb kinematics and measures of disease activity and disease impact could have been explored in the context of predictive relationships rather than explanatory relationships. Longitudinally, it is plausible that metrics concerning disease activity, disease impact and joint kinematics and kinetics change over time. The explanatory relationship described in the present study may not remain constant over time. It is likely that some variables may demonstrate modified linear relationships depending upon when within the first two years these data are collected. Measuring the direction that these data travel in response to disease activity and

pharmacotherapy would have provided information concerning the way in which the lower limb responds to the presence of disease under current treat-to-target protocols.

8.8 Areas for future research

Several proposals are made concerning future investigative studies with the aim of further developing current knowledge and understanding of lower limb disease in RA. It is suggested that future research should be undertaken to verify the results of the present study for several reasons. Firstly, the difficulty in recruiting a sufficient number of early RA participants was highlighted in chapter 2 resulting in a reduced level of statistical power. It was therefore highlighted that the present study should be considered exploratory in nature. Portney and Watkins caution that insufficient statistical power may lead to the presence of type II error (Portney and Watkins, 2009). In the present study, angular rotations at the hip, knee and ankle did not demonstrate evidence of significant between-group differences. Whilst these findings may indeed characterise lower limb movement patterns in the those early RA participants recruited for the present study, it is possible that between-group differences in these parameters do indeed exist in the wider early RA population. Furthermore, low levels of self-reported physical impairment and moderate disease activity were also reported in the present study. To avoid self-selection bias, participants were recruited from consecutive out-patient clinics. It is still possible, however, that only the most compliant and physically unimpaired individuals volunteered to take part in the study. Determining significant differences in lower limb walking patterns in a larger, more disease heterogeneous group of early RA participants may be required to confirm the results of the present study.

Conducting a larger scale investigation may also help mitigate against the limitations of PCA. By decomposing the original data into a set of linear variates, PCA was used to locate underlying dimensions within the kinematic variables analysed. PCA is concerned only with establishing linear components within data and how a particular variable might contribute to that component. An assumption of PCA, however, is that it assumes that the data being analysed represents an entire population of interest, not a sample. A limitation of PCA is that conclusions are restricted to the sample collected and generalisations of results can be achieved only if further analysis that is undertaken in different samples reveals the same factor structures. It may be argued that as a result of the way in which PCA operates, there can only be a limited generalisability of results of the present study to those early RA participants recruited and not to the wider early RA population.

A characteristic of all motion analysis studies investigating the impact of RA in both established disease (Woodburn et al., 2002a, Woodburn et al., 2003, Woodburn et al., 2004, Turner et al., 2008) and early disease (Turner et al., 2008) is the use of cross-sectional study designs to make between-group comparisons. The present study is no exception. A limitation of this methodology is that it does not take into account that joint destruction in RA appears to result from the cumulative burden of inflammation over time. This may have important consequences concerning the pathogenesis of lower limb functional impairment. The evolution and progression of altered lower limb walking patterns in RA under the influence of disease activity has yet to be examined. As these features develop over time, their progression cannot be captured using a cross-sectional study design. For this reason, the point at which alterations in lower limb movement patterns become significantly different is uncertain.

The present study was of a comparative cross-sectional design. For this reason, when describing the relative strength of the relationship between each dependent and independent variable investigated, independent variables were seen as having an explanatory capacity rather than one which was predictive. Therefore, a further rationale for studying early disease longitudinally is that this may provide data on the predictive relationships between lower limb movement patterns and measures of disease activity and physical impairment over time. Studying lower limb kinetics and kinematics under the simultaneous influence of drug modified disease activity, may help identify changes in key parameters and determine predictor variables. Together, with the evaluation of musculoskeletal foot health interventional programs, new pathways of evaluation and care for patients with early RA could be developed. It is important to note, however, that as test-retest repeatability of variables was evaluated in a small number of participants on the same day, to allow future longitudinal investigations of walking patterns in early RA participants, it is important to re-evaluate the repeatability in a larger sample of participants tested on different days.

Whilst the present study is believed to be the first to quantify intersegmental coupling relationships in the foot in early RA, the approach used to explore intersegmental coupling patterns in study 3 does have its limitations. Though the mean value of the CoRP provides spatial information regarding how adjacent segments were coupled, it does not provide direct information as to how the underlying segments were coordinated. This is important as the co-ordination of intersegmental coupling angles has been shown to change through the stance phase of gait. A modified vector coding technique proposed by Chang et al., (2008) provides this data by classifying intersegmental coupling according to their temporal location within the gait cycle. Understanding exactly where in the gait cycle alterations in the amplitude and variation in coupling actions take place may provide further data on the temporal components

of mechanical tissue stress in early RA. Such data would also inform and enhance the use of treatment interventions designed to alter biomechanical function.

A final consideration is that long term outcomes in RA may be differentiated according to gender. Although not addressed in the present study, gender dimorphism is known to modulate disease activity. The age of onset, disease pattern, frequency of destructive joint disease and frequency of extra-articular involvement are taken into account, women exhibit more aggressive disease outcomes (Lahita., 1996). These observations raise the possibility that gender modifies disease progression and prognosis. Indeed, it has been suggested that that male and female variants of RA may represent qualitatively different disease processes (Rubtsov et al., 2010). Gender also appears to influence therapeutic interventions in RA, with female patients developing more structural deformities requiring surgical intervention, possibly due to either gender-specific mechanical factors or gender specific differences in tissue composition (Gossec et al., 2005).

As a result of gender dimorphism, when long term outcomes are measured through pain and disability, the impact of RA on quality of life cannot be assumed to be the same for men and women. Women report higher levels of pain and physical disability associated with non-employment (Lahita, 1996b). Further investigation specifically evaluating the impact of gender on the characteristics of lower limb physical impairment in RA may provide unique data allowing a greater customisation of treatment interventions in individuals living with early RA

8.9 Conclusion

Through the present study, robust protocols for the evaluation of lower limb walking patterns in adults with early RA using 3D motion capture, measures of disease activity and measures of physical impairment in early RA have been defined. Using these protocols it was shown that in a group of early RA participants with low disease activity and low levels of self-reported physical impairment, when compared to age and gender matched controls, significant differences in the kinematics of the lower limb were seen. These differences were located at the distal extremity within the foot and were largely independent of current measures of disease activity.

Owing to the difficulties in recruitment, sampling bias and the limitations of the research design, the findings of this thesis should be interpreted on the basis of this research being exploratory in nature and therefore subject to further investigation. However, based upon these findings, the multidisciplinary use of 3D motion capture is recommended to meet both current and future demands for the early assessment and targeted management of mechanically based foot pathology in RA.

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Appendix I: Ethical Approval

21 August 2015

Dear Alexander,

Project Title:	**What is the impact of early adult rheumatoid arthritis on the biomechanical and functional characteristics of the foot and lower limb?**
Researcher(s):	**Alexander Izod**
Principal Investigator:	**Alexander Izod**

I am writing to confirm that the application for the aforementioned NHS research study reference **13/LO/0093** has received UREC ethical approval and is sponsored by the University of East London.

The lapse date for ethical approval for this study is **21 August 2019**. If you require UREC approval beyond this date you must submit satisfactory evidence from the NHS confirming that your study has current NRES ethical approval and provide a reason why UREC approval should be extended.

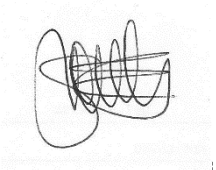
Please note as a condition of your sponsorship by the University of East London your research must be conducted in accordance with NHS regulations and any requirements specified as part of your NHS ethical approval.

Please confirm that you have conducted your study in accordance with the consent given by the NHS Ethics Committee by emailing researchethics@uel.ac.uk.

Please ensure you retain this approval letter, as in the future you may be asked to provide proof of ethical approval.

With the Committee's best wishes for the success of this project.

Yours sincerely,



Catherine Heulleteau
Research Integrity and Ethics Manager
For and on behalf of
Professor Neville Punchard
University Research Ethics Committee (UREC)
Research Ethics
Email: **researchethics@uel.ac.uk**

Appendix II: Participant Information

Information Sheet About the Research Study

Study Title: Gait and Function in Rheumatoid Arthritis (GAFRA) Study

We would like to invite you to take part in a PhD research study. Before you decide whether or not you would like to take part in this study it is important for you to understand what the purpose of this study is and how it will be conducted. One of our team will go through this information sheet with you and answer any questions you may have. We would suggest that this will take approximately 15 minutes.

What is the purpose of this study?

This study will measure whether rheumatoid arthritis causes changes to occur in the movement patterns of the foot and leg during walking and whether these movement patterns change over time. This study will also investigate whether or not any changes seen in these movement patterns are related to the wider effect of rheumatoid arthritis on the rest of the body.

Why have you been invited to take part in this study?

The research team are recruiting participants who have recently been diagnosed with rheumatoid arthritis. You have received this leaflet because you have recently been diagnosed with rheumatoid arthritis.

Do you have to take part in this study?

All participants are being recruited on a voluntary basis so it is entirely up to you whether or not you wish to take part in this study.

In what way will you be asked to participate in this study?

In order to investigate whether movement patterns in the foot and leg change over time, all participants are being invited to attend two study visits. The first study visit will take place

approximately one month following your initial diagnosis of rheumatoid arthritis. The second study visit will be scheduled to take place approximately three months following your initial diagnosis.

If you are interested in taking part in this study you will receive a letter by post which will invite you to attend an appointment at the Motion Analysis Laboratory (Room UH 207), University of East London, School of Health and Bioscience, Stratford Campus, Romford Road, London E15 4L.

At the first appointment you will meet the Chief Investigator (Alexander Izod) who will talk to you about this study and answer any questions that you may have.

Once you have spoken to the Chief Investigator, if you would still like to take part, you will be asked to read and sign a consent form which will give us your permission to include you as a participant in this study.

You are under no obligation to take part in this study. If you decide not to take part you will be able to leave the appointment and will not be asked to take any further part in this study.

At this appointment, if you agree to give us your permission to include you as a participant in this study, we would like to assess how rheumatoid arthritis may have affected the way in which you perform some basic daily activities. This will be done in several ways and during this assessment we will measure the following:

- How far you can walk in 6 minutes at your normal walking speed.
- The time it takes for you to stand up from a chair, walk a distance of 3 metres (10 feet), turn and then walk back to the same chair and sit down.
- Your grip strength by gripping onto a hand held device called a dynamometer. This is a portable instrument which measures how strong your grip is when you grip onto it.
- How long it takes you to fasten and unfasten buttons on a shirt that we will provide.
- The movement patterns of your feet, legs and pelvis.
- At the beginning of the recording session you will be asked to wear a pair of shorts in order to allow a set of small reflective markers to be placed on your feet, legs and pelvis. These reflective markers will be attached to the skin using an adhesive tape.
- After this, you will then be asked to walk at your normal speed along a walkway. As you do this the movement that takes place in your feet, legs and pelvis will be recorded using a set of cameras designed to detect the reflective markers.
- Human movement is very complex and difficult to study so you will be asked repeat all of these activities several times so that enough information can be recorded for analysis.

- At the end of this appointment you will be you will be asked to complete two questionnaires. The first questionnaire will ask you about the impact of rheumatoid arthritis on your foot health. The second questionnaire will ask you about the impact of rheumatoid arthritis on your ability to perform basic daily activities such as dressing, grooming or walking.

- This appointment will take approximately 2 ½ hours.

At the end of the first appointment you will be invited to take part in a second study visit. At this second study visit we will repeat all of the above measurements.

Are there any benefits to taking part in this study?

No. Although the Chief Investigator is a podiatrist registered with the Health and Care Professions Council, you will not be offered, or should expect to receive, any form of medical consultation or treatment.

Participation in this study is not intended to supplement or substitute for any medical or complimentary therapies that you may currently be receiving.

This study is not designed to directly or indirectly have a positive benefit on any aspect of your health and wellbeing.

What are the risks to you as a participant?

It is not unusual for people living with Rheumatoid Arthritis to experience pain, stiffness, muscle weakness and impaired movement. You will only be asked to complete activities in a manner that you find comfortable. If at any point you feel discomfort, you should inform the Chief Investigator and the testing will be stopped.

As a participant, will you receive any payment for taking part in this study?

No. However, your travel fees to the appointment will be reimbursed.

Can participants leave the study?

Yes. You do not have to give a reason for leaving this study and you may leave the study at any point with no disadvantage to yourself. Any information collected up until that point may be used as part of the study.

Is there any personal information about you that may be needed to carry out this study?

In order to assess the impact of rheumatoid arthritis on the movement patterns of your feet and legs, it will be necessary for the Chief Investigator (Alexander Izod) to access your hospital records. The Chief Investigator will only make a note of information that is relevant to the study. This will consist of the following information:

- Your date of birth and gender
- The date when you were first diagnosed
- The clinical presentation of your rheumatoid arthritis
- Any medications that you may be currently taking for rheumatoid arthritis

How will confidentiality be maintained?

Your contribution to this study and any data collected will be treated as strictly confidential information and stored in accordance with the Data Protection Act. Only information that is necessary to carry out this study will be collected. Only authorised persons will be able to access the information collected about you as part of this study.

The results of this study will be published for scientific benefit. No personal information about you will be identifiable from any scientific publications. The results will be available to you on request.

Who will know about your participation in this study?

Apart from the Chief Investigator and his academic supervisors, only your rheumatology consultant and nurse will know that you have been invited to participate in this study. If you consent, they will be informed of your participation. All information about you that is collected as part of this study will be stored in a locked cupboard. To ensure anonymity, your name and address will be removed from any files that are stored. Only members of the research team will be able to access the information collected about you.

Data collected on the questionnaire about your foot health may be shared with the developers of this questionnaire at Leeds University in order to monitor its use. All data will be anonymous and it will not be possible to identify you from any data that is shared.

Who is organising the funding of this research?

This research is being undertaken as part of a PhD research programme supervised by the School of Health, Sport and Bioscience at the University of East London. It is being funded by the Dr William M Scholl Podiatric Research and Development Fund.

Who has reviewed this research study?

This study has been reviewed and given ethical approval by the National Research Ethics Service (NRES) Committee London - Bloomsbury. It has also been reviewed and approved by the University of East London Research Ethics Committee.

Who do you contact if you want to find out more about this study?

If you would like to know more about this study, please speak to your rheumatology consultant or nurse. Alternatively, you can contact the Chief Investigator or his Director of Studies at the following addresses:

Chief Investigator

Alexander Izod

University of East London,

School of Health and Bioscience,

Room AE4.47,

Stratford Campus,

Water Lane, London E15 4LZ

(Telephone 0208 223 4339 e-mail a.izod@uel.ac.uk)

Director of Studies

Professor Wendy Drechsler

Associate Dean: Research and Knowledge Exchange

School of Health, Sport and Bioscience,

Room AE5.21,

Stratford Campus,

Water Lane, London, E15 4LZ

(Telephone 020 8223 4121 e-mail w.drechsler@uel.ac.uk)

Appendix III: Participant Consent

Subject Consent Form December 2012

Participant Study Number …….

Participant Consent Form

Research Project Title: Gait and Function in Rheumatoid Arthritis (GAFRA) Study

Chief Investigator: Alexander Izod

I have read the information leaflet relating to the above programme of research in which I have been asked to participate and have been given a copy to keep. The nature and purposes of the research have been explained to me, and I have had the opportunity to discuss the details and ask questions about this information. I understand what is being proposed and the procedures in which I will be involved have been explained to me.

I understand that my involvement in this study, and particular data from this research, will remain strictly confidential. Only the researchers involved in the study will have access to the data. I understand that relevant data collected during this study may be looked at by individuals from regulatory bodies, NHS Trusts participating in this study or by other universities. It has been explained to me what will happen to the data once the research programme has been completed.

It has been explained to me that, for the purposes of this study, personal information from my medical records will need to be accessed. I understand why this information is required and consent for this information to be accessed and used solely for the purpose of this study.

I hereby fully and freely consent to participate in the study which has been fully explained to me.

Having given this consent I understand that I have the right to withdraw from the programme at any time without disadvantage to myself and without being obliged to give any reason.

Participant's name (BLOCK CAPITALS):
.....
Participant's signature:
.....
Date……
Chief Investigator's name (BLOCK CAPITALS):
.....
Chief Investigator's signature:
.....
Date: ……

If you have any questions about this study, please contact the Director of Studies at the following address:

Professor Wendy Drechsler
Associate Dean: Research and Knowledge Exchange
School of Health, Sport and Bioscience,
Room AE5.21,
Stratford Campus,
Water Lane, London, E15 4LZ
(Telephone 020 8223 4121 e-mail w.drechsler@uel.ac.uk)

Appendix VI: Data Collection Sheet

Gait and Function in Rheumatoid Arthritis (GAFRA) Study

Participant Number……..

Initials…….. DOB……..

Date…….

Study Visit……..

Anthropometric Measurements

Height (cm)		
Weight (Kg)		
	Left	Right
Ankle (cm)		
Knee (cm)		
Leg Length (cm)		

Rheumatology Function Tests

	Left			Right		
	1	2	3	1	2	3
Grip Strength (Kg)						

	1	2	3
Timed Up and Go (Sec)			
Timed Button Test (Sec)			
Six Minute Walk Test (M)	2 Minutes: 6 Minutes:		

Appendix V: Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE

Participant Study Number _____

Date of assessment (dd/mm/yy)_____ Assessment number_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces, and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐

-Lift a full cup or glass to your mouth? ☐ ☐ ☐ ☐

-Open a milk carton? ☐ ☐ ☐ ☐

WALKING

Are you able to:

-Walk outdoors on flat ground? ☐ ☐ ☐ ☐

-Climb up five steps? ☐ ☐ ☐ ☐

Please check any AIDS OR DEVICES that you usually use for any if these activities:

☐ Cane ☐ Devices used for dressing (button hook, zipper pull, shoe horn, etc.)

☐ Walker ☐ Special or built up utensils

☐ Crutches ☐ Special or built up chair

☐ Wheelchair ☐ Other (specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and Grooming ☐ Eating

☐ Arising ☐ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
HYGENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath	☐	☐	☐	☐
-Get on and off the toilet	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐

ACTIVITIES

Are you able to:

-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork?	☐	☐	☐	☐

Please check any AIDS or DEVICES that you usually use for any activities:

☐ Raised toilet seat

☐ Bathtub bar

☐ Bathtub seat

☐ Long-handled appliances for reach

☐ Jar opener (for jars previously opened)

☐ Long-handled appliances in bathroom

☐ Other (specify_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene

☐ Gripping and opening things

☐ Reach

☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A <u>VERTICAL</u>|( ) MARK ON THE LINE TO INDICATE THE SEVERITY OF PAIN

NO PAIN	**SEVERE PAIN**
0	**100**

Appendix VI: Summary tables of test-retest repeatability

Table A(VI) 1: Repeatability of spatial-temporal parameters

	Phase 1				*Phase 2*			
Parameter	Mean ± SD	Mean Diff	SEM	ICC	Mean ± SD	Mean Diff	SEM	ICC
Cadence (steps/min)	109.18 ± 16.51	0.06	3.58	0.95	108.07 ± 12.51	0.06	2.58	0.95
Step Length (mm)	679.05 ± 48.76	1.59	18.18	0.86	672.05 ± 48.76	1.59	16.15	0.83
Stride Length (mm)	1331.61 ± 86.96	3.70	29.10	0.89	1311.41 ± 84.42	3.68	28.10	0.84
Walking Speed (mm/s)	1282.78 ± 198.25	5.53	44.77	0.95	1280.72 ± 198.25	5.51	43.52	0.92
Toe-off (%)	58.33 ± 1.65	0.12	0.79	0.77	58.31 ± 1.61	0.11	0.71	0.73

Table A(VI) 2: Repeatability of sagittal plane kinematic parameters at the hip, knee and ankle

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland and Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland and Altman LOA
Hip	Initial Contact	33.36 ± 4.80	1.90	-0.95	0.95	3.09 →- 4.90	33.19 ± 7.03	1.11	0.26	0.93	28.98 → 38.02
	Toe-off	-2.49 ± 4.95	1.04	-0.38	0.95	3.74 → -4.46	0.17 ± 5.30	0.38	0.47	0.78	0.08 → 0.20
	Peak extension	-9.68 ± 6.52	-0.46	1.11	0.97	3.99 →- 4.89	-7.38 ± 4.89	0.02	0.39	0.85	-3.34 → -10.72
	Peak flexion	33.44 ± 5.84	-0.09	1.77	0.91	5.1 → 8.03	35.75 ± 7.03	1.16	0.26	0.93	31.09 → 40.07
	Total ROM	-43.52 ± 6.67	-0.31	1.25	0.96	5.39 → -4.78	-43.13 ± 4.95	1.19	0.32	0.90	-38.72 → -47.86
Knee	Initial Contact	5.81 ± 3.35	1.01	-0.30	0.90	3.64 →- 4.23	8.04 ± 3.67	0.53	0.41	0.83	6.05 → 11.08
	Toe-off	36.41 ± 4.74	1.49	0.93	0.89	8.16 → -6.32	36.68 ± 4.94	0.63	0.58	0.66	29.87 → 41.02
	Peak flexion	56.88 ± 8.81	0.16	3.08	0.88	11.49 → -11.17	3.50 ± 4.07	2.10	0.32	0.90	-1.03 → 5.74
	Peak extension	1.99 ± 5.11	0.24	2.04	0.83	7.99 → -7.53	58.72 ± 6.65	1.02	0.36	0.87	53.89 → 61.74
	Total ROM	54.88 ± 5.88	1.96	3.10	0.77	9.18 → -2.07	-55.22 ± 5.32	1.08	0.44	0.81	-50.00 → -54.72
Ankle	Initial Contact	-1.22 ± 3.91	1.50	0.62	0.86	4.31 → -3.07	-3.65 ± 3.88	0.89	0.53	0.72	-0.42 → -5.34
	Toe-off	-9.22 ± 4.82	1.90	0.64	0.84	7.63 → -6.36	-14.81 ± 5.68	1.40	0.42	0.82	-12.87 → -16.02
	Peak dorsiflexion	12.69 ± 4.48	-0.69	1.27	0.92	4.54 → -4.69	-18.06 ± 4.66	0.64	0.47	0.78	-16.74 → -20.56
	Peak plantarflexion	-14.87 ± 3.95	-0.28	2.54	0.61	8.02 → -8.60	13.34 ± 4.37	0.41	0.22	0.95	11.07 → 14.31
	Total ROM	27.55 ± 5.72	-0.43	2.37	0.84	7.96 → -8.80	-31.40 ± 5.26	1.05	0.42	0.82	-29.04 → -32.01

Table A(VI) 3: Repeatability of frontal plane kinematic parameters at the hip, knee and ankle

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland &Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA
Hip	Initial Contact	-2.20 ± 2.23	0.93	0.33	0.82	3.75 → -3.12	-1.76 ± 3.58	1.10	0.45	0.80	-0.90 → -2.75
	Toe-off	-5.36 ± 3.45	0.73	0.28	0.95	3.18 → -2.65	-5.86 ± 4.48	0.05	0.28	0.92	-1.07 → -7.77
	Peak Adduction	4.60 ± 2.53	0.37	0.99	0.83	4.17 → -3.30	-6.86 ± 4.08	0.56	0.24	0.94	-3.56 → -8.04
	Peak Abduction	-4.71 ± 2.08	-0.02	0.61	0.91	2.33 → -2.36	6.32 ± 4.08	0.07	0.26	0.93	3.65 → 7.72
	Total ROM	9.25 ± 3.74	0.46	1.12	0.90	4.86 → -3.97	-13.18 ± 3.47	0.63	0.40	0.84	-9.90 → -14.02
Knee	Initial Contact	1.40 ± 2.76	0.96	-0.16	0.85	3.61 → -3.92	0.40 ± 4.21	0.10	0.26	0.93	-2.00 → 0.65
	Toe-off	0.87 ± 3.59	1.37	-0.42	0.86	3.88 → -4.71	3.66 ± 11.30	2.43	0.22	0.95	7.85 → 4.21
	Peak Valgus	0.44 ± 3.69	-0.53	1.17	0.90	3.74 → -4.78	-7.73 ± 9.83	3.55	0.14	0.98	-3.98 → -10.84
	Peak Varus	4.58 ± 6.09	-0.52	1.98	0.90	6.94 → -7.96	13.62 ± 10.54	1.17	0.30	0.91	3.03 → 17.32
	Total ROM	6.28 ± 4.66	-0.63	1.30	0.92	14.79 → -15.40	-21.35 ± 8.40	3.32	0.32	0.90	-17.56 → -24.12
Ankle	Initial Contact	-0.98 ± 2.46	1.37	0.42	0.76	3.57 → -2.73	-3.05 ± 3.55	0.54	0.24	0.94	-2.90 → -4.78
	Toe-off	0.21 ± 3.29	0.75	-0.11	0.85	2.84 → -3.06	-1.48 ± 3.02	0.60	0.32	0.90	-0.21 → -2.89
	Peak Inversion	3.16 ± 1.59	-0.37	0.56	0.87	1.69 → -2.45	-4.69 ± 3.29	0.85	0.36	0.87	-1.74 → -6.67
	Peak Eversion	-1.11 ± 1.95	-0.44	1.10	0.78	2.83 → -3.72	2.41 ± 2.30	0.29	0.36	0.87	2.35 → 3.81
	Total ROM	3.93 ± 2.74	0.76	1.03	0.76	3.10 → -3.01	-7.10 ± 1.86	0.56	0.68	0.54	-5.78 → -8.00

Table A(VI) 4: Repeatability of transverse plane kinematic parameters at the hip knee and ankle

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland &Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA
Hip	Initial Contact	-6.04 ± 11.93	-0.31	4.04	0.88	10.19 → -8.73	-12.89 ± 8.40	0.99	0.20	0.96	-3.98 → -18.04
	Toe-off	1.61 ± 11.50	-0.08	3.89	0.88	11.23 → -9.69	0.80 ±17.65	4.33	0.26	0.93	-8.45 → 17.95
	Peak Ext Rotation	-11.03 ± 2.22	0.53	0.56	0.85	14.23 → -11.44	-23.74 ± 4.99	3.96	0.26	0.93	-14.78 → -29.02
	Peak Int Rotation	10.21 ± 12.80	4.58	4.08	0.89	11.38 → -8.22	10.80 ± 18.07	0.93	0.26	0.93	9.73 → 21.02
	Total ROM	-22.27 ± 5.82	0.84	2.19	0.82	8.07 → -6.40	-34.54 ± 9.69	3.03	0.53	0.72	-31.87 → -38.92
Knee	Initial Contact	-1.91 ± 5.53	2.52	2.52	0.76	11.61 → -6.68	-12.11 ± 9.89	2.84	0.44	0.81	-8.09 → -15.31
	Toe-off	2.11 ± 5.75	1.68	0.28	0.89	7.15 → -7.70	-5.32 ± 9.58	0.28	0.52	0.73	-3.74 → -7.22
	Peak Ext Rotation	6.56 ± 5.97	-0.01	1.80	0.91	6.75 → -6.77	-17.89 ± 0.85	0.68	0.39	0.85	-9.67 → -20.71
	Peak Int rotation	-6.93 ± 5.57	0.52	2.52	0.69	11.44 → -10.43	5.90 ± 10.48	0.77	0.32	0.90	1.89 → 7.84
	Total ROM	13.73 ± 7.15	0.80	2.46	0.87	9.54 → -9.82	-23.79 ± 6.72	0.08	0.44	0.81	-25.12 → -27.41
Ankle	Initial Contact	1.93 ± 5.41	1.52	0.32	0.91	6.45 → -5.82	12.34 ± 13.75	3.95	0.32	0.90	0.04 → 11.02
	Toe-off	-0.43 ± 6.34	2.38	0.36	0.87	8.32 → -9.05	5.34 ± 11.92	3.85	0.46	0.79	1.07 → 10.59
	Peak Adduction	-7.92 ± 4.79	-0.17	2.53	0.73	8.68 → -9.03	-13.08 ± 8.98	3.65	0.42	0.82	-6.02 → 15.03
	Peak Abduction	9.15 ± 9.14	1.43	4.22	0.82	15.48 → -12.56	19.91 ± 11.90	3.79	0.47	0.78	15.81 → 21.85
	Total ROM	14.56 ± 14.32	-1.68	7.31	0.75	15.73 → -12.60	-32.99 ± 5.93	0.14	0.55	0.70	-32.01 → -33.87

Table A(VI) 5: Waveform symmetry analysis of hip, knee and ankle kinematics

		Phase 1				*Phase 2*			
Segment	*Plane*	*Trend Symmetry (unitless)*	*Range Amplitude (unitless)*	*Range Offset (°)*	*Phase Offset (%)*	*Trend Symmetry (unitless)*	*Range Amplitude (unitless)*	*Range Offset (°)*	*Phase Offset (%)*
Hip	Sagittal	0.99	1.02	0.05	-1	0.99	1.02	0.05	-1
Knee	Sagittal	0.99	1.02	0.23	1	0.99	1.02	0.23	1
Ankle	Sagittal	0.99	1.02	-0.42	-1	0.99	1.02	-0.46	-1
Hip	Frontal	0.99	0.95	0.67	N/A	0.99	0.95	0.67	N/A
Knee	Frontal	0.98	0.90	-0.35	N/A	0.97	0.90	-0.34	N/A
Ankle	Frontal	0.99	1.01	-0.37	N/A	0.97	1.02	-0.37	N/A
Hip	Transverse	0.98	1.02	-0.31	N/A	0.98	1.01	-0.21	N/A
Knee	Transverse	0.99	-0.92	-0.95	N/A	0.99	0.91	-0.91	N/A
Ankle	Transverse	0.99	0.88	2.77	N/A	0.99	0.87	2.68	N/A

Table A(VI) 6: Repeatability of sagittal plane kinematic parameters at the shank-calcaneus and calcaneus-midfoot

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA
Shank-Calcaneus	Initial Contact	-1.40 ± 6.22	0.77	0.55	0.99	2.50 → -0.97	-10.77 ± 5.40	0.93	0.35	0.88	-15.67 → -5.29
	Toe-off	-11.09 ± 6.32	0.83	0.59	0.99	2.56 → -0.90	9.80 ± 4.68	2.13	0.32	0.90	5.79 → 12.02
	Peak Extension	-15.31 ± 3.31	0.81	0.57	0.97	2.46 → -0.85	23.39 ± 5.27	0.08	0.17	0.97	19.45 → 26.67
	Peak Flexion	4.08 ± 5.25	0.81	0.57	0.99	2.46 → -0.84	12.61 ± 4.59	0.16	0.36	0.87	8.71 → 14.82
	Total ROM	19.24 ± 3.85	-0.11	2.73	0.98	3.99 → 0.73	8.22 ± 3.3	0.24	0.28	0.88	6.79 → 10.56
Calcaneus-Midfoot	Initial Contact	25.59 ± 6.89	-1.81	0.99	0.98	0.31 → -3.86	27.43 ± 5.96	1.81	0.48	0.77	21.56 → 27.34
	Toe-off	20.39 ± 9.23	-1.79	0.99	0.99	0.32 → -3.83	21.31 ± 6.69	1.37	0.47	0.78	19.45 → 24.34
	Peak Extension	18.66 ± 9.87	-1.84	1.02	0.99	0.31 → -3.91	30.21 ± 5.09	2.06	0.33	0.89	28.33 → 32.91
	Peak Flexion	33.39 ± 6.43	-1.83	0.99	0.98	0.28 → -3.85	17.75 ± 6.59	2.10	0.55	0.70	15.91 → 19.43
	Total ROM	14.61 ± 4.32	-0.24	2.08	0.98	2.04 → 0.49	12.46 ± 3.62	0.03	0.55	0.70	10.21 → 13.74

Table A(VI) 7: Repeatability of planar angles at the MLA and first MPJ

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA
MLA	Initial Contact	140.13 ± 12.43	-1.08	2.19	0.87	117.03 → 164.65	136.59 ± 9.72	2.72	0.33	0.89	127.82 →140.43
	Toe-off	151.05 ± 13.52	-0.12	0.61	0.80	125.80 → 179.92	142.94 ± 10.40	2.79	0.28	0.92	139.56 →149.72
	Peak Flexion	152.83 ± 13.75	-0.73	1.39	0.89	125.54 → 179.84	152.18 ± 9.40	2.52	0.40	0.84	145.12 →160.24
	Peak Extension	130.93 ± 11.87	-0.97	1.70	0.88	108.73 → 155.57	131.25 ± 6.74	4.43	0.46	0.79	128.24 → 39.72
	Total ROM	21.44 ± 11.07	2.52	2.77	0.75	13.87 → 29.01	20.93 ± 7.48	1.92	0.62	0.61	15.98 → 25.52
First MPJ	Initial Contact	31.40 ± 4.50	-1.54	1.96	0.81	-1.30 → 8.40	34.92 ± 5.96	0.20	0.14	0.98	25.82 → -41.35
	Toe-off	61.35 ± 15.31	-2.65	2.65	0.97	-0.73 → 9.40	29.12 ± 25.89	2.92	0.61	0.63	23.72 → 35.82
	Peak dorsiflexion	67.44 ± 10.91	-3.43	5.56	0.74	-3.98 → 13.2	3.21 ± 4.85	6.32	0.50	0.75	3.02 → 7.28
	Peak plantarflexion	2.79 ± 3.63	-0.49	1.15	0.90	-2.91 → 9.00	73.93 ± 25.46	0.23	0.20	0.96	70.67 → 84.56
	Total ROM	46.21 ± 11.46	-2.81	4.86	0.82	11.2 → 30.1	77.14 ± 43.54	6.55	0.20	0.96	65.72 → 80.32

Table A(VI) 8: Repeatability of transverse plane kinematic parameters at the shank-calcaneus and calcaneus-midfoot

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA
Shank-Calcaneus	Initial Contact	-13.12 ± 4.13	1.61	1.74	0.82	7.55 → -4.32	-12.30 ± 4.66	0.72	0.55	0.70	-8.23 → -15.81
	Toe-off	-14.95 ± 5.84	2.14	3.10	0.72	3.65 → 0.62	-9.36 ± 3.37	0.30	0.62	0.62	-7.04 → -4.81
	Peak abduction	-18.14 ± 4.15	1.74	2.05	0.75	8.78 → -5.31	-7.72 ± 3.90	1.19	0.47	0.78	-5.65 → -9.34
	Peak adduction	-9.65 ± 3.52	1.52	1.31	0.86	5.71 → -2.67	-15.31 ± 4.45	0.47	0.48	0.77	-12.78 → -16.27
	Total ROM	-8.48 ± 3.03	1.46	1.43	0.78	4.84 → -1.30	7.59 ± 2.04	0.72	0.66	0.57	8.35 → 4.92
Calcaneus-Midfoot	Initial Contact	-2.10 ± 6.25	-2.58	0.53	0.99	0.91 → -2.40	9.84 ± 5.90	1.01	0.32	0.90	3.09 → 12.43
	Toe-off	-0.96 ± 6.69	-1.42	0.56	0.99	0.96 → -2.53	8.65 ± 5.75	0.72	0.42	0.82	6.92 → 12.04
	Peak abduction	-3.71 ± 6.52	-4.30	0.59	0.99	0.85 → -2.51	13.51 ± 6.10	1.67	0.55	0.70	7.43 → 19.08
	Peak adduction	-0.02 ± 6.54	-0.45	0.55	0.99	0.81 → -2.45	4.75 ± 5.56	0.26	0.33	0.89	1.09 → 8.79
	Total ROM	3.69 ± 0.10	-0.02	0.52	0.98	1.60 → -0.40	8.76 ± 2.94	1.40	0.61	0.63	7.23 → 10.07

Table A(VI) 9: Waveform symmetry analysis of shank-calcaneus, calcaneus-midfoot, MLA and first MPJ kinematics

		Phase 1				*Phase 2*			
	Plane	*Trend Symmetry (unitless)*	*Range Amplitude (unitless)*	*Range Offset (°)*	*Phase Offset (%)*	*Trend Symmetry (unitless)*	*Range Amplitude (unitless)*	*Range Offset (°)*	*Phase Offset (%)*
Shank-Calcaneus	Sagittal	0.98	0.84	-0.65	1	0.98	0.84	-0.65	1
Calcaneus-Midfoot	Sagittal	0.95	0.56	3.56	-1	0.95	0.56	3.56	-1
Shank-Calcaneus	Transverse	0.97	0.54	1.05	N/A	0.97	0.54	1.05	N/A
Calcaneus-Midfoot	Transverse	0.94	0.63	-3.61	N/A	0.94	0.63	-3.61	N/A
Shank-Calcaneus	Frontal	0.94	0.58	-1.63	N/A	0.94	0.58	-1.63	N/A
Calcaneus-Midfoot	Frontal	0.97	0.45	-1.89	N/A	0.97	0.45	-1.89	N/A
MLA	Sagittal	0.99	1.08	-2.65	-1	0.99	1.08	-2.65	-1
First MPJ	Sagittal	0.92	0.97	1.57	-2	0.92	0.97	1.57	-2

Table A(VI) 10: Repeatability of sagittal plane kinetic parameters at the hip, knee and ankle

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA
Hip	Initial Contact	0.40 ± 0.12	0.02	0.05	0.82	0.32 → 0.51	0.40 ± 0.12	0.02	0.06	0.77	0.32 → 0.58
	Toe-off	-0.40 ± 0.14	-0.04	0.07	0.74	-0.28 → -0.31	-0.40 ± 0.30	-0.08	0.16	0.70	0.30 → 0.55
	Midstance	-0.20 ± 0.13	0.00	0.00	0.83	-0.07 → -0.08	-0.40 ± 0.16	-0.04	0.08	0.73	-0.18 → -0.23
	Peak extension	-1.30 ± 0.65	-0.12	0.37	0.68	-1.89 → -1.00	-1.30 ± 0.65	-0.12	0.39	0.65	-0.01 → -1.20
	Peak flexion	0.76 ± 0.13	0.00	0.03	0.93	0.89 → 1.03	0.76 ± 0.14	0.00	0.06	0.80	0.39 → 0.89
Knee	Initial Contact	-0.16 ± 0.08	0.01	0.02	0.95	-0.18 → -0.23	-0.16 ± 0.08	0.01	0.02	0.95	-0.21 → -0.20
	Toe-off	0.13 ± 0.11	0.01	0.04	0.88	0.08 → 0.28	0.22 ± 0.27	0.06	0.12	0.81	-0.04 → 0.35
	Midstance	-0.09 ± 0.14	0.02	0.05	0.87	-0.03 → -0.23	0.13 ± 0.10	0.01	0.04	0.84	-0.03 → 0.23
	Peak Extension	-0.45 ± 0.07	-0.02	0.03	0.82	-0.41 → -0.50	-0.45 ± 0.08	-0.02	0.03	0.80	-0.36 → -0.51
	Peak flexion	0.78 ± 0.44	0.11	0.24	0.70	0.38 → 1.09	0.78 ± 0.09	0.11	0.05	0.70	-0.69 → 0.80
Ankle	Initial Contact	-0.04 ± 0.06	0.00	0.02	0.90	-0.03→-0.08	-0.03 ± 0.08	0.01	0.04	0.75	0.00 → 0.01
	Toe-off	-0.01 ± 0.07	0.00	0.02	0.90	-0.01→-0.09	0.40 ± 0.11	-0.02	0.06	0.68	0.30 → 0.48
	Midstance	-0.01 ± 0.03	0.00	0.01	0.83	-0.00→-0.06	-0.01 ± 0.07	0.00	0.03	0.79	0.00 → 0.04
	Peak plantarflexion	-0.16 ± 0.10	-0.02	0.05	0.80	-0.10→-0.18	-0.16 ± 0.11	-0.02	0.05	0.78	-0.08 → 0.11
	Peak dorsiflexion	1.06 ± 0.62	-0.07	0.35	0.68	0.89→1.12	1.06 ± 0.63	-0.07	0.38	0.64	1.01 →1.40

Table A(VI) 11: Repeatability of frontal plane kinetic parameters at the hip, knee and ankle

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland & Altman LOA
Hip	Initial Contact	0.11 ± 0.14	0.06	0.08	0.72	0.05 → 0.19	0.11 ± 0.14	0.06	0.08	0.72	-0.01 → -0.05
	Toe-off	-0.07 ± 0.13	-0.02	0.06	0.78	-0.01 → 0.02	0.48 ± 0.28	0.01	0.15	0.72	0.15→ 0.21
	Midstance	0.13 ± 0.06	0.01	0.02	0.87	0.03 → 0.15	-0.07 ± 0.13	-0.02	0.07	0.72	-0.10 → 0.08
	Peak adduction	-0.14 ± 0.06	-0.03	0.03	0.72	-0.08 → -0.20	0.13 ± 0.06	0.01	0.03	0.81	0.08 → 0.19
	Peak Abduction	0.85 ± 0.37	0.04	0.16	0.82	0.47 → 0.92	-0.14 ± 0.06	-0.03	0.03	0.71	-0.16 → -0.12
Knee	Initial Contact	0.06 ± 0.08	0.03	0.03	0.85	0.02 → 0.18	0.85 ± 0.37	0.04	0.17	0.80	0.13 → 0.04
	Toe-off	-0.02 ± 0.04	0.00	0.01	0.89	-0.01 → -0.09	0.06 ± 0.08	0.03	0.04	0.80	0.03 → 0.10
	Midstance	0.07 ± 0.04	0.01	0.01	0.88	0.02 → 0.08	0.21 ± 0.20	-0.03	0.09	0.80	0.01→ 0.30
	Peak Adduction	-0.06 ± 0.03	-0.01	0.01	0.80	-0.02 → -0.07	-0.02 ± 0.04	0.00	0.02	0.69	-0.03 → 0.03
	Peak Abduction	0.48 ± 0.25	0.02	0.13	0.73	0.29 → 0.64	0.06 ± 0.04	0.00	0.02	0.78	0.08 → 0.08
Ankle	Initial Contact	0.02 ± 0.05	0.01	0.01	0.91	0.01→ 0.06	-0.06 ± 0.03	-0.01	0.01	0.76	-0.07 → 0.00
	Toe-off	0.02 ± 0.02	0.01	0.01	0.88	0.01 → 0.03	0.32 ± 0.25	-0.14	0.14	0.70	-0.15 → 0.15
	Midstance	0.00 ± 0.01	0.00	0.00	0.89	-0.01 → 0.01	0.02 ± 0.05	0.01	0.02	0.81	0.00 → 0.00
	Peak adduction	-0.05 ± 0.05	-0.01	0.01	0.97	-0.02 → -0.07	0.04 ± 0.14	0.02	0.09	0.65	0.05 → 0.04
	Peak abduction	0.13 ± 0.19	0.03	0.10	0.69	0.09 → 0.23	0.02 ± 0.02	0.01	0.01	0.74	0.02 → 0.01

Table A(VI) 12: Repeatability of transverse plane kinetic parameters at the hip, knee and ankle

		Phase 1					*Phase 2*				
Segment	Parameter	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland and Altman LOA	Test Mean (°) ±SD	Mean Difference	SEM	ICC	Bland and Altman LOA
Hip	Initial Contact	-0.01 ± 0.01	0.00	0.00	0.92	-0.00 → -0.02	-0.01 ± 0.01	0.00	0.01	0.82	-0.00 → - 0.02
	Toe-off	0.02 ± 0.01	0.00	0.00	0.88	0.01 → 0.03	0.00 ± 0.03	-0.01	0.02	0.78	-0.01 → 0.02
	Midstance	-0.01 ± 0.01	0.00	0.00	0.77	-0.01 → -0.02	0.02 ± 0.01	0.00	0.01	0.80	0.03 → 0.01
	Peak ext rota	-0.15 ± 0.08	-0.02	0.04	0.72	-0.13 → -0.17	-0.15 ± 0.09	-0.02	0.05	0.70	-0.016 → 0.04
	Peak int rota	0.10 ±0.05	0.00	0.02	0.85	0.08 → 0.12	0.10 ± 0.05	0.00	0.02	0.80	0.13 → 0.04
Knee	Initial Contact	0.00 ± 0.01	0.00	0.00	0.90	-0.01 → 0.01	0.00 ± 0.01	0.00	0.00	0.79	-0.01 → 0.01
	Toe-off	0.01 ± 0.01	0.00	0.00	0.88	0.02 → 0.01	0.05 ± 0.06	0.00	0.03	0.78	-0.01 → 0.08
	Midstance	0.00 ± 0.01	0.00	0.00	0.90	-0.01→ 0.00	0.01 ± 0.01	0.00	0.01	0.72	-0.02 → 0.01
	Peak ext rota	-0.03 ± 0.01	0.00	0.01	0.78	-0.02 → -0.01	-0.03 ± 0.01	0.00	0.01	0.72	-0.05 → 0.00
	Peak int rota	0.14 ± 0.08	0.01	0.04	0.79	0.08 → 0.16	0.14 ± 0.09	0.01	0.05	0.72	-0.15 → 0.05
Ankle	Initial Contact	0.00 ± 0.00	0.00	0.00	0.93	0.00 → 0.00	0.00 ± 0.00	0.00	0.00	0.83	0.00 → 0.00
	Toe-off	0.01 ± 0.01	0.00	0.00	0.89	0.00 → 0.02	0.04 ± 0.04	0.00	0.02	0.70	0.05 → 0.04
	Midstance	0.00 ± 0.01	0.00	0.00	0.89	-0.01 → 0.01	0.01 ± 0.01	0.00	0.01	0.79	0.02 → 0.01
	Peak ext rota	-0.03 ± 0.01	0.00	0.01	0.76	-0.02 → 0.00	-0.03 ± 0.01	0.00	0.01	0.77	-0.04 → 0.01
	Peak int rota	0.10 ± 0.06	0.00	0.02	0.89	0.08 → 0.12	0.10 ± 0.06	0.00	0.03	0.81	-0.11 → 0.01

Table A(VI) 13: Phase 1 Individual criterion item fit for FPI-6 (n=10)

	Test 1				*Test 2*			
	New Difficulty Logit	Item Standard Error	Person Standard Error	Infit MnSq	New Difficulty Logit	Item Standard Error	Person Standard Error	Infit MnSq
Talar Head	0.19	0.88	0.91	1.18	1.30	0.86	0.93	1.03
Malleoli	0.17	1.04	0.90	0.81	2.02	0.86	0.90	1.09
Rearfoot	0.17	0.78	0.91	1.08	2.02	0.86	0.90	1.06
T-N joint	0.00	0.79	0.90	0.81	1.30	0.86	0.90	0.90
MLA	0.33	0.83	0.90	0.90	4.07	1.11	0.93	0.36
FF Abduction	0.50	0.79	0.93	1.04	0.69	0.93	0.98	1.09

Table A(VI)14: Phase 2 Individual criterion item fit for FPI-6 (n=25)

	Test 1				*Test 2*			
	New Difficulty Logit	Item Standard Error	Person Standard Error	Infit MnSq	New Difficulty Logit	Item Standard Error	Person Standard Error	Infit MnSq
Talar Head	1.97	0.45	0.58	1.05	1.80	1.06	1.02	1.05
Malleoli	1.22	0.91	0.17	1.14	1.73	1.15	0.51	1.03
Rearfoot	2.04	0.96	1.08	0.68	2.60	1.17	1.02	1.03
T-N joint	1.09	0.83	1.05	1.08	1.39	0.97	1.08	0.99
MLA	1.55	0.66	0.90	0.71	1.85	1.06	1.82	0.72
FF Abduction	1.97	0.45	1.04	0.91	1.49	1.02	1.10	0..68

Table A(VI) 16: Phase 1 conversion of raw FPI-6 scores into Rasch transformed scores (n=10)

Phase 1					
Test 1 Raw FPI-6 Score	Test 1 FPI-6 score Frequency	Transformed FPI-6 Score	Test 2 Raw FPI-6 Score	Test 2 FPI-6 Score Frequency	Transformed FPI-6 Score
0.00	1	0.00	-2.00	1	-1.41
2.00	3	0.25	0.00	1	0.00
3.00	3	2.28	2.00	2	1.21
6.00	1	4.32	3.00	3	2.30
9.00	1	5.61	6.00	1	4.09
10.00	1	6.84	8.00	1	5.71
			10.00	1	7.01

Table A(VI) 17: Phase 2 conversion of raw FPI-6 scores into Rasch transformed scores (n=25)

Phase 2					
Test 1 Raw FPI-6 Score	Test 1 FPI-6 score Frequency	Transformed FPI-6 Score	Test 2 Raw FPI-6 Score	Test 2 FPI-6 Score Frequency	Transformed FPI-6 Score
0.00	3	0.00	-1.00	1	-1.41
2.00	14	0.35	-1.00	13	0.00
3.00	3	2.71	2.00	4	1.31
5.00	2	4.52	3.00	3	2.36
8.00	2	5.21	5.00	1	4.19
7.00	1	5.94	7.00	2	5.81
			9.00	1	6.02