Measurement of Physical Activity and its impact on Inflammatory Markers linked to Cardiovascular Disease in Rheumatoid Arthritis

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A thesis submitted to the University of Limerick in fulfilment of the requirements for the award of Doctor of Philosophy

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Submitted to the University of Limerick, January 2013.
ABSTRACT

The studies which compose this thesis stem from two literature reviews. The first literature review determined that definitive conclusions regarding physical activity levels in the RA population and how they compare to a control population cannot be determined due mainly to methodological concerns in the studies in the area, in particular the use of subjective and/or unvalidated physical activity measurement tools. The second literature review concluded that a link exists between inflammation and the increased risk of cardiovascular disease in the RA population. Furthermore, a link was also found between physical activity and inflammation and cardiovascular disease in populations other than the RA population. However, limited research has been conducted in the RA population to determine if a link exists between physical activity and inflammation.

Thus, initially a study was designed to assess the validity of an objective physical activity measurement tool to estimate physical activity in the RA population. The findings of this research determined that the SWA provides an accurate measure of energy expenditure in this population. This tool was then utilised in studies which assessed physical activity in the population.

Studies were designed and undertaken to assess energy expenditure levels in the RA population, assess how these levels compared to a control population and determine some correlates of energy expenditure in the population.

A study was also designed and undertaken to assess the relationship between a wide range of inflammatory markers which are known to be linked to cardiovascular disease, and energy expenditure in the RA population.

Two further studies were also undertaken in order to complement the previously mentioned studies. Firstly, a study was designed to assess the validity of a frequently used subjective physical activity measurement tool when compared to the SWA in the RA population. Users’ experiences of having their health, in particular their physical activity levels, monitored in the home through technological means were also assessed as part of this thesis.
DECLARATION

I declare that this thesis is entirely my own work and that it has not been submitted at this or any other University or higher education institution for any academic award.

Where use has been made of the work of other people, it has been fully acknowledged and referenced.

Signed: ______________________

Date:    ______________________
ACKNOWLEDGEMENTS

To my supervisors, Dr. Norelee Kennedy and Dr. Alexander Fraser, thank you for your constant support, advice and encouragement in all aspects of this project. Your help has always been most gratefully appreciated.

To the Irish Research Council and Intel Ireland for the awarding of my postgraduate scholarship, without which this project could not have been undertaken. I would also like to express my thanks to the Central Remedial Clinic, Irish Rheumatology Health Professionals Society, Western Branch of Irish Society of Chartered Physiotherapists and Roche for allowing me the opportunity to disseminate my research nationally and internationally.

To the staff of the Clinical Therapies department at the University of Limerick for advice and assistance during this process.

To Dr. Helen Purtill, for her input into the statistical analysis of the data.

To my fellow postgrads, past and present, who have always enhanced this process.

To all who assisted me with the SHIMMER – Dr. Cliodhna Ni Scannaill, Adrian Burns, Dr. Emma Fortune and Niall Twomey.

To all the staff at the Mid Western Regional Hospitals who assisted me with regard to data collection, the rheumatology team, the dermatology team and the staff at the Dept. of Pathology. In particular, thanks needs to go to the nursing staff at the outpatients’ clinic in Croom, Dr. Bart Ramsey at the Dept. of Dermatology and Mary Tobin at the Dept. of Pathology.

To Dr. Ursula Fearon and Dr. Jennifer McCormick at the Conway Institute for Bimolecular and Biomedical Research, University College, Dublin for assistance with blood marker analysis.

To my family and friends for their patience and encouragement over the duration of this process. I couldn’t have done it without your support.
Finally above all else, I want to say a special thank you to Adrian. Your constant strength, support, encouragement and constant belief in me, even when I didn’t believe in myself, will never be forgotten. I don’t think I will never be able to aptly express my gratitude for all you have done.
# Table of Contents

ABSTRACT ........................................................................................................................ III

DECLARATION ................................................................................................................... IV

ACKNOWLEDGEMENTS ................................................................................................. V

LIST OF TABLES ........................................................................................................... XIII

LIST OF FIGURES ........................................................................................................ XIV

CHAPTER 1 THESIS OUTLINE ...................................................................................... 1

1.1 BACKGROUND TO THESIS .................................................................................... 2
1.2 THESIS AIM ............................................................................................................. 2
1.3 THESIS OBJECTIVES ............................................................................................ 2
1.4 THESIS SUMMARY .................................................................................................. 3

CHAPTER 2 GENERAL INTRODUCTION ...................................................................... 5

2.1 RHEUMATOID ARTHRITIS ....................................................................................... 6
2.2 EPIDEMIOLOGY OF RA ........................................................................................ 6
2.3 RHEUMATOID CACHEXIA ....................................................................................... 7
2.4 PHYSICAL ACTIVITY .............................................................................................. 8
   2.4.1 What is Physical Activity? ................................................................................. 8
   2.4.2 Benefits of Physical Activity ............................................................................ 9
   2.4.3 Barriers to Physical Activity in RA ................................................................. 10
2.5 MEASUREMENT OF PHYSICAL ACTIVITY .......................................................... 10
   2.5.1 Step Count ........................................................................................................ 11
   2.5.2 Energy Expenditure ........................................................................................ 11
   2.5.3 Energy Expenditure in RA .............................................................................. 13
   2.5.4 Calculation of REE, TEF and PAEE ............................................................... 14
   2.5.5 Number of days ............................................................................................... 14
   2.5.6 Seasonality and Weather conditions ............................................................ 15
2.6 MEASUREMENT TOOLS ...................................................................................... 16
   2.6.1 Subjective Measures ....................................................................................... 16
   2.6.2 Objective Measures ...................................................................................... 17
      2.6.2.1 Direct observation .................................................................................... 17
      2.6.2.2 Pedometers ............................................................................................ 18
      2.6.2.3 Accelerometers ....................................................................................... 18
      2.6.2.4 Doubly labelled water ............................................................................ 19
      2.6.2.5 Calorimetry ............................................................................................. 20
      2.6.2.6 Multi-location accelerometers .............................................................. 20
      2.6.2.7 Multi-sensor devices .............................................................................. 20
   2.6.2.7.1 SWA ................................................................................................. 20
2.7 CONCLUSION .......................................................................................................... 21

SECTION 1: .................................................................................................................... 23

CHAPTER 3 PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW ........................................................................................................... 25
3.1 INTRODUCTION ......................................................................................................................... 26
3.2 METHODOLOGY .......................................................................................................................... 26
3.3 RESULTS ...................................................................................................................................... 29
3.4 DISCUSSION ................................................................................................................................. 39
  3.4.1 Measurement Tools .................................................................................................................. 39
  3.4.2 Terminology ............................................................................................................................ 40
  3.4.3 Comparison to national guidelines .......................................................................................... 41
3.5 RECOMMENDATIONS FOR FUTURE RESEARCH ................................................................. 42
3.6 LIMITATION ................................................................................................................................. 42
3.7 CONCLUSION ............................................................................................................................... 43

CHAPTER 4 CARDIOVASCULAR RISK, INFLAMMATION AND PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS .................................................. 45
  4.1 INTRODUCTION .......................................................................................................................... 46
  4.2 REASONS FOR THE INCREASED RISK OF CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS ................................................................. 46
  4.3 INFLAMMATION AND INFLAMMATORY MARKERS AND THE LINKS TO CARDIOVASCULAR DISEASE RISK ................................................................. 49
  4.4 EFFECT OF PHYSICAL ACTIVITY ON INFLAMMATORY MARKERS IN OTHER POPULATIONS ......................................................................................... 52
  4.5 EFFECT OF PHYSICAL ACTIVITY ON INFLAMMATORY MARKERS IN RHEUMATOID ARTHRITIS ......................................................................................... 58
  4.6 CONCLUSION ............................................................................................................................... 59

CHAPTER 5 A STUDY TO DETERMINE THE CRITERION VALIDITY OF THE SENSEWEAR ARMBAND AS A MEASURE OF PHYSICAL ACTIVITY IN PEOPLE WITH RHEUMATOID ARTHRITIS ........................................ 61
  5.1 INTRODUCTION .......................................................................................................................... 62
  5.2 METHODOLOGY .......................................................................................................................... 63
    5.2.1 Subjects .................................................................................................................................. 63
    5.2.2 SenseWear Armband (SWA) ................................................................................................. 63
    5.2.3 Video Observation .................................................................................................................. 63
    5.2.4 Indirect Calorimetry ................................................................................................................ 64
  5.3 PROTOCOL .................................................................................................................................... 64
  5.4 DATA PROCESSING ...................................................................................................................... 65
    5.4.1 SWA ...................................................................................................................................... 65
    5.4.2 Oxycon Mobile ....................................................................................................................... 65
  5.5 DATA ANALYSIS ......................................................................................................................... 66
  5.6 RESULTS ...................................................................................................................................... 67
    5.6.1 Step Count .............................................................................................................................. 67
    5.6.2 Energy Expenditure ................................................................................................................ 69
  5.7 DISCUSSION .................................................................................................................................. 70
    5.7.1 Step Count .............................................................................................................................. 71
    5.7.2 Energy Expenditure ................................................................................................................ 72
  5.8 LIMITATIONS ............................................................................................................................... 74
CHAPTER 6 GENERAL METHODOLOGY ................................................. 79

6.1 ETHICAL APPROVAL ................................................................. 80

6.2 SUBJECT RECRUITMENT ........................................................ 80
   6.2.1 RA subjects ....................................................................... 80
   6.2.2 Control subjects ............................................................... 81

6.3 PROTOCOL FOR USING SWA TO MEASURE ENERGY EXPENDITURE ... 84
   6.3.1 Application of the SWA .................................................... 84
   6.3.2 Monitoring period ............................................................. 84

6.4 SWA DATA REDUCTION .......................................................... 85
   6.4.1 Valid day and Imputation ................................................ 85
   6.4.2 Number of Valid days ...................................................... 86
   6.4.3 Final units of measurement .............................................. 88

6.5 RECORDING PERIOD ............................................................... 88

6.6 DEMOGRAPHIC AND DISEASE RELATED VARIABLES .................... 89
   6.6.1 Demographic Variables .................................................... 89
   6.6.2 Disease related variables ................................................ 89

6.7 INFLAMMATORY BLOOD MARKERS ............................................ 92
   6.7.1 Procedure ....................................................................... 92
   6.7.2 White Cell Count ............................................................ 92
   6.7.3 C Reactive Protein .......................................................... 92
   6.7.4 Fibrinogen ..................................................................... 92
   6.7.5 Erythrocyte Sedimentation Rate ..................................... 93
   6.7.6 Interleukin-6 and Interleukin-8 ........................................ 93
   6.7.7 Interleukin-10 ................................................................. 93
   6.7.8 Serum Amyloid A ........................................................... 93
   6.7.9 Tumor Neurosis Factor - α .............................................. 93

6.8 CHOLESTEROL SAMPLE .......................................................... 94

CHAPTER 7 A PROFILE OF ENERGY EXPENDITURE AND IT’S
CORRELATES IN THE RHEUMATOID ARTHRITIS POPULATION AND A
COMPARISON WITH DISEASE CONTROLS ......................................... 95

7.1 INTRODUCTION ........................................................................ 96

7.2 METHODOLOGY ...................................................................... 97

7.3 DATA ANALYSIS ...................................................................... 97
   7.3.1 Transformations ............................................................... 98
     7.3.1.1 Profile of energy expenditure in RA ......................... 98
     7.3.1.2 Comparison of energy expenditure levels to controls ... 98
     7.3.1.3 Regression Analysis ................................................. 98
   7.3.2 Statistical Analysis .......................................................... 98
     7.3.2.1 Profile of Energy Expenditure in RA ................. 98
     7.3.2.2 Comparison of Energy Expenditure Levels to Controls 99
     7.3.2.3 Regression Analysis ................................................. 99

7.4 RESULTS ............................................................................... 100
   7.4.1 Demographic Profile ....................................................... 100
   7.4.2 Profile of energy expenditure in RA ............................... 102
CHAPTER 8 THE RELATIONSHIP BETWEEN ENERGY EXPENDITURE AND INFLAMMATORY MARKERS IN THE RHEUMATOID ARTHRITIS POPULATION ............................................................... 125

8.1 INTRODUCTION ........................................................................................................... 126
8.2 METHODOLOGY .......................................................................................................... 127
8.3 DATA ANALYSIS ......................................................................................................... 127
  8.3.1 Transformations ........................................................................................................ 127
  8.3.2 Statistical Analysis ................................................................................................... 128
8.4 RESULTS ....................................................................................................................... 129
  8.4.1 Bivariate Analysis ................................................................................................... 130
  8.4.2 Multivariate Analysis ............................................................................................... 132
  8.4.2.1 Model 1 (age, BMI and Smoking controlled for) ...................................................... 134
  8.4.2.2 Model 2 (Age, BMI, Cholesterol, DAS-28, Gender, Smoking (and Statin Use for CRP only) controlled for) ............................................................. 135
8.5 DISCUSSION ................................................................................................................. 135
8.6 STRENGTHS ................................................................................................................ 138
8.7 LIMITATIONS ............................................................................................................... 138
8.8 FUTURE RESEARCH .................................................................................................. 138
8.9 CONCLUSION ............................................................................................................... 139

CHAPTER 9 CRITERION VALIDITY OF THE INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ) FOR USE IN THE RA POPULATION: COMPARISON WITH THE SENSEWEAR ARMBAND ... 141

9.1 INTRODUCTION ........................................................................................................... 142
9.2 METHODOLOGY ........................................................................................................ 143
  9.2.1 General methodology ............................................................................................. 143
  9.2.2 International Physical Activity Questionnaire (IPAQ) – Short Form ......................... 143
9.3 DATA ANALYSIS ........................................................................................................ 144
  9.3.1 Transformations .................................................................................................... 144
  9.3.2 Statistical Analysis ................................................................................................ 145
9.4 RESULTS ..................................................................................................................... 146
  9.4.1 Concurrent Validity of the IPAQ–SF: overall physical activity level ......................... 147
  9.4.2 Concurrent Validity of the IPAQ–SF: specific levels of intensity ............................... 148
  9.4.2.1 Sitting Time ...................................................................................................... 148
  9.4.2.2 Walking Time .................................................................................................. 148
  9.4.2.3 Vigorous Time .................................................................................................. 148
APPENDIX A: CRITERION VALIDITY OF SHIMMER IN RA.................................225
APPENDIX B: MODIFIED NEWCASTLE OTTAWA SCALE.................................239
APPENDIX C: INFORMATION SHEETS, CONSENT FORMS AND INFORMATION BOOKLET AND DIARY ...........................................................................................................................................................................241
APPENDIX D: DATA COLLECTION FORM (TENDER COUNT, SWOLLEN COUNT, VISUAL ANALOG SCALE AND HEALTH ASSESSMENT QUESTIONNAIRE).................................265
APPENDIX E: INTERNATION PHYSICAL ACTIVITY QUESTIONNAIRE SHORT FORM (IPAQ-SF)...........................................................................................................................................................................269
APPENDIX F: SPSS OUTPUT .................................................................................................................273
LIST OF TABLES

TABLE 3.1 DESCRIPTIVE CHARACTERISTICS OF STUDIES INCLUDED IN REVIEW ........ 30
TABLE 3.2 METHODOLOGY AND OVERALL RESULTS OF INCLUDED STUDIES ............ 32
TABLE 3.3 QUALITY OF STUDIES INCLUDED IN REVIEW ..................................... 37
TABLE 4.1 METHODOLOGY AND OVERALL RESULTS OF STUDIES ......................... 54
TABLE 5.1 DESCRIPTIVE CHARACTERISTICS OF STUDY PARTICIPANTS .................. 67
TABLE 5.2 BLAND AND ALTMAN TABLE FOR STEP COUNT (SWA) ......................... 68
TABLE 5.3 BLAND AND ALTMAN TABLE FOR ENERGY EXPENDITURE (SWA) .......... 69
TABLE 6.1 SUMMARY OF RESULTS OF ALMEDIA ET AL. (2011) STUDY .................. 87
TABLE 6.2 BREAKDOWN OF INDIVIDUALS NUMBER OF CONSECUTIVE VALID DAYS .. 88
TABLE 7.1 DESCRIPTIVE CHARACTERISTICS OF STUDY SUBJECTS ...................... 101
TABLE 7.2 SOCIODEMOGRAPHIC PROFILE OF STUDY SUBJECTS ......................... 101
TABLE 7.3 ENERGY EXPENDITURE PROFILE FOR WEEKDAYS AND WEEKEND DAYS .... 102
TABLE 7.4 ENERGY EXPENDITURE PROFILE OF RA INDIVIDUALS ....................... 103
TABLE 7.5 COMPARISON OF ENERGY EXPENDITURE VALUES IN RA AND CONTROL POPULATIONS ................................................................. 106
TABLE 7.6 CORRELATIONS BETWEEN ENERGY EXPENDITURE AND POTENTIAL CORRELATES ........................................................................... 110
TABLE 7.7 MODELS OF BEST FIT FOR ENERGY EXPENDITURE VARIABLES .......... 111
TABLE 8.1 DESCRIPTIVE CHARACTERISTICS OF STUDY SUBJECTS ...................... 129
TABLE 8.2 TOTAL GROUP CORRELATIONS BETWEEN ENERGY EXPENDITURE VARIABLES AND INFLAMMATORY MARKERS (RECIPROCAL TRANSFORMATIONS ACCOUNTED FOR) .......................................................... 131
TABLE 8.3 MALE GROUP CORRELATIONS BETWEEN ENERGY EXPENDITURE VARIABLES AND INFLAMMATORY MARKERS (RECIPROCAL TRANSFORMATIONS ACCOUNTED FOR) .......................................................... 131
TABLE 8.4 FEMALE GROUP CORRELATIONS BETWEEN ENERGY EXPENDITURE VARIABLES AND INFLAMMATORY MARKERS (RECIPROCAL TRANSFORMATIONS ACCOUNTED FOR) .......................................................... 131
TABLE 8.5 VARIANCE EXPLAINED BY ENERGY EXPENDITURE VARIABLES IN EACH MODEL ................................................................................. 133
TABLE 9.1 DESCRIPTIVE CHARACTERISTICS OF STUDY SUBJECTS ...................... 147
TABLE 9.2 CORRELATIONS BETWEEN SWA OUTPUTS AND IPAQ-SF OUTPUTS .... 149
TABLE 9.3 PAEE VALUES FOR SWA AND IPAQ-SF ................................................. 150
TABLE 9.4 CORRELATIONS BETWEEN SWA PAEE OUTPUT AND IPAQ PAEE OUTPUT ................................................................................. 150
TABLE 10.1 QUESTIONING ROUTE ........................................................................ 165
TABLE 10.2 DEMOGRAPHIC PROFILE OF GROUPS OF PARTICIPANTS ................. 166
TABLE 10.3 DEMOGRAPHIC PROFILE OF EACH PARTICIPANT .............................. 167
LIST OF FIGURES

Figure 2.1 Visual Representation of Total Energy Expenditure (TEE) .... 12
Figure 3.1 Flow Chart Outling Methodology .................................................. 28
Figure 5.1 Bland and Altman plot for total step count (SWA) .............. 68
Figure 5.2 Bland and Altman plot for Total Energy Expenditure (SWA)
................................................................................................................................. 70
Figure 6.1 Flow Diagram of RA Subjects Recruitment ................... 81
Figure 6.2 Flow Diagram of Dermatology Subjects Recruitment ........ 83
Figure 7.1 Total Energy Expenditure Breakdown for total sample (Fig.
7.1A), male sample (Fig. 7.1B) and female sample (Fig. 7.1C)............. 108
Figure 9.1 Bland and Altman Plo for PAEE (Total Sample) ............... 151
Figure 9.2 Bland and Altman Plot for PAEE (Male Sample) .............. 152
Figure 9.3 Bland and Altman Plot for PAEE (Female Sample) ........... 152
CHAPTER 1 THESIS OUTLINE
1.1 BACKGROUND TO THESIS
Rheumatoid Arthritis is a chronic, systemic, autoimmune inflammatory disease. Cardiovascular disease is the leading cause of mortality in this population (Solomon et al. 2003, Turesson et al. 2004, Wolfe et al. 2005), mainly attributable to inflammatory reasons (Del Rincón et al. 2001, Peters et al. 2010). Physical activity is known to impact upon inflammation levels in many population groups, but this relationship has not been investigated thoroughly in the RA population. Furthermore, physical activity levels, or the correlates of physical activity has not been determined definitively in the RA population. Validation of physical activity measurement tools is necessary to ensure the accuracy of the output. Objective tools are preferable to subjective tools due to the risk of bias with the latter; however subjective tools are often better accepted by the users. The experience of use of objective monitoring tools is also important to determine their future utilisation.

1.2 THESIS AIM
To provide valid data on the profile of physical activity in the RA population and to explore the role that physical activity plays on inflammation related cardiovascular disease in this population.

1.3 THESIS OBJECTIVES
The main objectives of this thesis were as follows:

1. To systematically review the literature involving physical activity in rheumatoid arthritis.

2. To review the current literature regarding links between cardiovascular risk, inflammation and physical activity, particularly in rheumatoid arthritis.

3. To examine the criterion validity of two objective physical activity measurement tools in the rheumatoid arthritis population

4. To profile the energy expenditure levels and the correlates of energy expenditure of the rheumatoid arthritis population and compare levels of energy expenditure to a control population.
5. To investigate the relationship between energy expenditure levels and inflammatory markers known to be related to cardiovascular disease in the rheumatoid arthritis population.

6. To quantitatively explore the experiences of home monitoring, particularly with regard to physical activity monitoring tools in the rheumatoid arthritis population.

7. To examine the criterion validity of a subjective physical activity measurement tool for use in the rheumatoid arthritis population.

1.4 Thesis Summary

Chapter 2 outlines background information regarding rheumatoid arthritis. Its diagnosis, classification, epidemiology and the concurrent disorder of rheumatoid cachexia are described. Chapter 2 also outlines background information regarding physical activity; in particular its components, benefits and measurement issues are portrayed.

Chapter 3 presents a systematic review conducted to examine physical activity levels in the RA population and how these levels compare to control populations.

Chapter 4 presents an understanding of the reasons for the increased cardiovascular disease risk in the rheumatoid arthritis population. It also outlines the links between inflammation, in particular inflammatory markers and cardiovascular disease risk. Furthermore, the role that physical activity plays in the modulation of inflammatory markers in both the general and other clinical population is described, and what is known on the topic in the RA population is also discussed.

Chapter 5 presents the criterion validity of the SenseWear Armband for both step count and energy expenditure to estimate activities of daily living in the rheumatoid arthritis population.

Chapter 6 presents the general methodology for the studies relayed in Chapters 7 and 8. In particular, the analysis conducted on the data to produce energy expenditure output is described as well as details regarding the recruitment, protocol and other variables recorded.
Chapter 7 profiles the energy expenditure levels of the rheumatoid arthritis population and compares them to that of a disease control population. Reference is also made to how the levels recorded for the rheumatoid arthritis population compare to levels previously reported in the literature.

As physical activity is a modifiable behaviour, Chapter 7 also examines the demographic and health related correlates of energy expenditure in the rheumatoid arthritis population and also presents a model which best predicts energy expenditure in this population. These classes of correlates are those which have been less well investigated in the rheumatoid arthritis population.

Chapter 8 investigates the relationship which exists between energy expenditure levels and inflammatory markers known to be related to cardiovascular disease in rheumatoid arthritis. A wider range of inflammatory markers than those which have been previously examined were investigated in this study.

Chapter 9 presents details of the criterion validity of the International Physical Activity Questionnaire - Short Form (IPAQ-SF), which is a subjective physical activity measurement tool, to estimate free living habitual physical activity in the rheumatoid arthritis population.

Chapter 10 reports on the users experiences of home monitoring, particularly in relation to physical activity monitoring technology in the rheumatoid arthritis population.

Chapter 3, 4, 5 and 10 have been published in peer review journals and details of these publications have been outlined in the relevant chapters. Some amendments have been made to these publications in order to aid the presentation and readability of the thesis. Copyright permission with regard to this published work has been sought and obtained from the relevant publishers.
CHAPTER 2 GENERAL INTRODUCTION
2.1 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic, systemic, autoimmune disorder which is inflammatory in nature, being the most common of the inflammatory arthritides. The clinical manifestations of RA are highly variable. Symmetric arthritis affecting the metacarpalphalageal (MCP) and proximal interphalageal (PIP) joints is the most characteristic early clinical feature, but as the disease progresses further joints typically become implicated (Robbins et al. 2001). The number of joints involved is highly variable, but generally the disease is polyarticular in nature. Almost any joint may be affected (Robbins et al. 2001, Ruddy and Kelley 2005) but there is a predisposition for peripheral joints with sparing of the axial skeleton with the exception of the cervical spine. The most commonly affected joints are the MCP and PIP joints of the hands, wrists, elbows, ankles, metatarsalphalageal joints of the feet and the temporalmandibular joints (Fleming et al. 1976). Involvement of the shoulder, hip or sternoclavicular joints are less common. In conjunction with joint pain, there is swelling with associated stiffness, warmth and tenderness with a characteristic morning accentuation of symptoms (Adebajo 2010, Ruddy and Kelley 2005, Hakim 2010). Edema and proliferation of the synovium contribute to stiffness by mechanically interfering with joint motion. Although RA is characterised primarily by joint involvement, it is a systemic inflammatory disorder and most individuals also experience systemic symptoms such as fatigue, malaise and low grade fever (Adebajo 2010, Ruddy and Kelley 2005, Hakim 2010).

2.2 Epidemiology of RA

RA is a worldwide phenomenon however several varying prevalence and incidence rate results have been reported, suggesting a considerable variation in the disease occurrence among differing populations. The Institute of Public Health in Ireland reported that 169,000 persons are estimated to have a doctor diagnosis of Rheumatoid Arthritis in the Republic of Ireland (InstituteofPublicHealthinIreland 2012).

The majority of prevalence studies conducted in Northern European and North American area estimate a prevalence of 0.5 – 1.1%. Studies from Southern European
countries report a prevalence rate of 0.3 – 0.7% while developing countries report a prevalence of between 0.1 and 0.5% (Alamanos and Drosos 2005). A prevalence rate of 5% has been reported in the Pima and Chippewa Native American populations (Hochberg and Spector 1990).

Annual incidence rates have not been as thoroughly investigated but appear to follow a similar pattern to that of the prevalence rates with rates of 0.02 – 0.05% found in North American and Northern European area with lower rates determined in Southern European areas.

Numerous studies have indicated that there is increased mortality in patients with RA compared to the general population (approximately a 50% increase) (Aviña-Zubieta et al. 2008). Much of this increased mortality has been attributed to cardiovascular causes with gastrointestinal, respiratory, haematological and infectious diseases also causative (Mutru et al. 1985, Wolfe et al. 2005)

Women are affected up to five times more frequently than men and typically the onset of the disease tends to occur between the ages of 40 and 60 for both sexes (Ruddy and Kelley 2005, Adebajo 2010).

Although the search for a specific etiologic agent has been intensive, the cause of RA has not yet been discovered. Its pathogenesis is likely to be multifactorial, with genetic background contributing to susceptibility along with exposure to unknown environmental factors (Ruddy and Kelley 2005, Robbins et al. 2001).

2.3 Rheumatoid Cachexia

Rheumatoid cachexia is a concurrent metabolic disorder, affecting almost all of the RA population to some extent (Roubenoff 2008, Walsmith and Roubenoff 2002). The term refers to a loss of body cell mass (BCM) which leads to muscle weakness, a loss of functional capacity and increased morbidity.

A loss of greater than 40% of baseline BCM has been shown to be associated with mortality (Kotler et al. 1989), while even a 5% reduction leads to changes in morbidity factors, including reduced muscle strength, altered energy metabolism and
increased infection susceptibility (Roubenoff and Kehayias 1991). It has been shown that the average loss of BCM among individuals with RA is between 13 and 15% (Roubenoff et al. 1994, Roubenoff et al. 1992).

Rheumatoid cachexia, although referring to loss of BCM, is actually occurs without a loss of weight. In fact, loss of BCM in RA is accompanied by increased fat mass and maintenance of a stable weight. In individuals with RA, these changes predispose to a condition known as “rheumatoid cachectic obesity”.

The causes of rheumatoid cachexia have not been determined. It appears that the excessive production of TNF-α and IL-1β alter the balance between protein degradation and synthesis to cause muscle wasting (Roubenoff 2008, Metsios et al. 2007). Overproduction of TNF-α enhances protein catabolism, leading to loss of BCM and increased resting energy expenditure (Metsios et al. 2008a, Roubenoff et al. 2002).

2.4 Physical Activity

2.4.1 What is Physical Activity?

“Physical activity" and "exercise" are terms that describe different concepts. However, they are often confused with one another, particularly by health professionals, and the terms are sometimes used interchangeably. By definition, physical activity is ‘any bodily movement produced by skeletal muscles that results in energy expenditure’ (Caspersen et al. 1985). Under this broad concept, activities involving leisure-time, exercise, sport, transportation and work must be considered. Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective; the improvement or maintenance of physical fitness (Caspersen et al. 1985). Much of the research conducted to date in the RA population has focused on the effect of exercise training with benefits reported in functional ability and other RA-related disease outcomes (Cooney 2011, Cairns and McVeigh 2009, Metsios et al. 2008b). Much less work has been conducted in the broader category of physical activity.
2.4.2 Benefits of Physical Activity

Physical activity is one of the most modifiable determinants of chronic morbidity and total mortality (Lagerros et al. 2009, Gulsvik et al. 2011). Regular physical activity is associated with improved physical and mental health in all population groups. In population studies, regular physical activity is associated with reduced incidence of obesity, colon and breast cancers, cardiovascular diseases, thromboembolic stroke, hypertension, type 2 diabetes, osteoporosis, anxiety, depression and falls and injuries (Franco et al. 2005, Noda et al. 2005, Bauman 2004, Haskell et al. 2007, Katzmarzyk and Craig 2002). In all, the risk of all-cause mortality has been shown to be reduced by 30% in persons who partake in regular physical activity compared to their inactive counterparts (Crespo et al. 2002).

Furthermore, specific to the RA population, an ACR working group determined that some level of physical activity is necessary for the maintenance of joint health for both normal and arthritic joints (Chang et al. 2003). As previously outlined cardiovascular disease mortality is of major concern in the RA population. Traditional cardiovascular risk factors have been shown to be modulated by physical activity in the general population (Kohl 2001, Oguma and Shinoda-Tagawa 2004). However, physical activity and its affect on traditional cardiovascular disease risk factors have never been researched in any populations characterised by high grade systemic inflammation, including RA (Metsios et al. 2008b). As will be highlighted in Chapter 4, inflammation has been implicated in the pathogenesis of atherosclerosis and elevated levels are associated with increased cardiovascular disease risk. Physical activity appears to have an impact at reducing this cardiovascular disease risk, both in the general population and RA population.

In 1995, exercise specialists from the American College of Sports Medicine and Centers for Disease Control (ACSM/CDC) came together to issue a revised public health directive as evidence mounted that the health benefits (largely cardiovascular) associated with these formal exercise regimens also occurred with accumulated lifestyle physical activity (Pate et al. 1995). Their revised recommendation was for the accumulation of 30 minutes of moderate-intensity lifestyle physical activity in short segments (ten minute bouts) on most, if not all, days of the week (Haskell et al.
Furthermore, the American College of Rheumatology (ACR) also supports these recommendations for people with RA (Krebs 2003).

However, despite the benefits associated with physical activity, especially in the RA population, it appears that this population may display lower levels of physical activity than their healthy counterparts and the recommendations. These findings are outlined in Chapter 3.

2.4.3 Barriers to Physical Activity in RA

A number of issues have come to light which appear to act as barriers to physical activity and exercise in RA. Pain, stiffness, fatigue and mobility problems have been shown to influence physical activity behaviours in this population (Der Ananian et al. 2006, Wilcox et al. 2006, van Den Berg et al. 2008). Furthermore, age, gender, education, social support, perceived benefits and self efficacy also impact upon physical activity levels (van Den Berg et al. 2008, Eurenius et al. 2003, Fontaine and Haaz 2006, Shin et al. 2006, Greene et al. 2006). Also, highlighting the impact health professionals and in particular hospital consultants have upon patients beliefs, rheumatologists beliefs about the effectiveness of various forms of exercise play an important role in the promotion of physical activity behaviours among people with RA (Iversen et al. 2004).

Physical activity and exercise does not appear to cause any negative impact on the disease state of individuals with RA. A review conducted by de Jong and Vliet Vlieland (2005), found that even moderate and high level intensity weight bearing exercise has no detrimental effects on disease activity or the progression of radiologic damage of joints of the hands and the feet. The only recommendation that this review made was that intensive activity should be individualised for those people whom have significant radiological damage of large joints (de Jong and Vliet Vlieland 2005).

2.5 Measurement of Physical Activity

Physical activity is a concept rather than a quantifiable scientific unit (O'Dwyer and Coote 2010). It has many dimensions that can be measured and quantified as a proxy measure of physical activity (Warms 2006). These include energy expenditure, type,
frequency, intensity and duration of activity, distance covered or steps taken, or response to activity outcomes such as heart rate. However, no single proxy measure can fully represent physical activity when examined in isolation as physical activity is multi-dimensional in nature. The most commonly utilised of these measures are movement (e.g. step counts) and energy expenditure (Thomas et al. 2005). Expressing physical activity in terms of these measures appears logical given the definition of physical activity (Caspersen et al. 1985) contains both the terms “movement” and “energy expenditure”. However, inherent difficulties arise with the use of either of these measures.

2.5.1 Step Count
Measures of step count are particularly useful for the capturing of walking behaviours (Tudor-Locke and Myers 2001) and as many researchers consider the measurement of walking to be an adequate representation of physical activity due to the almost uniformity of its presence in the typical behaviour of ambulatory individuals and the knowledge that in ambulatory individuals, movement of upper extremities accounts only for a small proportion of total energy expenditure (Kumahara et al. 2004). However, the main limitation with the use of step counts as a measure of physical activity is that it does not account for the intensity of the activity undertaken, which is of distinct importance when quantifying the cardiovascular benefit of physical activity. Thus, the limiting of physical activity measurement solely to step count will provide an estimation of how much activity is occurring, but will not identify the intensity of this activity.

2.5.2 Energy Expenditure
Due to the limitations associated with the use of step count as a measure of physical activity, energy expenditure assessment has become increasingly popular. Energy expenditure is thought to provide a more accurate indication of physical activity due to its ability to encompass both upper and lower limb activities (O'Dwyer and Coote 2010) and its ability to account for intensity. It is important to note that there are three components to total energy expenditure (TEE): Basal metabolic rate (BMR), the thermic effect of food and physical activity related energy expenditure (PAEE). BMR is the energy expended when an individual is lying at complete rest, in the morning after sleep, in the post absorptive state (Levine 2007). Approximately 65%
of daily energy expenditure is accounted for by basal metabolic rate. Resting energy expenditure (REE) is a concept related to BMR and as it is generally within 10% of BMR, both terms are often used interchangeably. REE is measured as the energy expended at complete rest in the post absorptive state. The thermic response of food is the energy expended in activities related to the absorption, digestion, transport and storage of food. It typically accounts for about 10% of TEE. The remaining 25% of TEE is accounted for by physical activity (Levine 2007). This physical activity related energy expenditure (PAEE) is the most variable component of total energy expenditure and is the easiest to manipulate (Plasqui 2008) as well as being the component most of interest to physical activity researchers. The breakdown of TEE into its components is visually represented by Fig. 2.1.

FIGURE 2.1 VISUAL REPRESENTATION OF TOTAL ENERGY EXPENDITURE (TEE)
2.5.3 Energy Expenditure in RA

These percentages related to healthy individuals however and resting energy expenditure (REE) can be significantly altered by a number of factors including chronic inflammatory disease (Metsios et al. 2008a, Roubenoff et al. 2002, de Carvalho et al. 2004). RA is both an inflammatory disorder and one which is characterised by metabolic abnormalities. Rheumatoid cachexia is known to lead to increased REE (Metsios et al. 2008a, Roubenoff et al. 2002). Thus, if the percentage of TEE attributed to REE increases, it follows that the most modifiable component, PAEE, will decrease correspondingly. Therefore, if an individual with RA expends a similar TEE value to that of a healthy individual, it is likely that the proportion of that TEE attributable to physical activity will be considerably less, a concept which is important to be aware of when comparing physical activity levels of the RA population to other populations. As has been previously outlined TEE (which is the output most commonly produced by objective physical activity measurement tools reporting on energy expenditure) is composed of three components: BMR/REE, TEF and PAEE. TEF is classically represented as 10% in a multitude of literature (Schutz et al. 1984, Poehlman et al. 1991, Westerterp 2004) and there does not to appear to be any evidence that this values differs for differing populations. PAEE is the modifiable component and differs between people depending on the activity completed.

REE in RA has been shown to be significantly different in the RA population than in the healthy population. Roubenoff et al. (1994) showed that REE was 12% higher (p<0.008) in RA subjects compared to healthy controls. Furthermore, it has been shown by (Metsios et al. 2008a) that the currently used prediction equations for the healthy populations are misleading in RA as they do not take into account the hypermetabolic processes occurring in RA and thus will under-predict the actual REE in RA. Therefore, it would be impossible to compare TEE between the RA population and controls, which have a normal REE, so as to accurately reflect how much physical activity is occurring. Instead, utilising PAEE will give a much more accurate reflection of this.
2.5.4 Calculation of REE, TEF and PAEE

In healthy subjects a number of equations have been formulated to evaluate REE. A recent systematic review (Frankenfield et al. 2005) recommends the use of Mifflin-St Joer equation as this was found to be the most reliable for representation of REE, and thus this equation was utilised for the control population. This is defined as:

\[
\text{Females: } (9.99 \times \text{weight}) + (6.25 \times \text{height}) - (4.92 \times \text{age}) - 161
\]

\[
\text{Males: } (9.99 \times \text{weight}) + (6.25 \times \text{height}) - (4.92 \times \text{age}) + 5
\]

However in RA, Metsios et al. (2008a) recommends use of a REE equation specific for use in the RA population due to the metabolic differences evident in this population. This equation is:

\[
598.8 \times \text{weight}^{0.47} \times \text{age}^{-0.29} \times \text{CRP}^{0.066}
\]

TEF has classically been represented as 10% of TEE in a multitude of literature (Westerterp 2004, Poehlman et al. 1991), with no indication made for the necessity of modification for the RA population.

Thus, PAEE is calculated using the formula:

\[
\text{PAEE} = \text{TEE} - \text{REE} - \text{TEF}
\]

2.5.5 Number of Days

The minimum number of days which subjects are required to wear monitors for has major implications with regard to compliance with the tool, as too long a period may prove too burdensome for the subject. However conversely, too short a period will not provide enough data to accurately represent the habitual level of activity.

Another issue which must be considered when discussing number of days of monitoring required is the “Hawthorne effect” and its implications. It is a general scientific fact that the process of observation alters the phenomenon being observed (Corder et al. 2008). The extent to which this is a problem depends on the degree of invasiveness of the measurement method (Brage et al. 2005). But it is an issue which must be dealt with in some manner in order to accurately reflect the outcome being monitored. Corder et al. (2008) outline that the behavioural modification caused by the act of being monitored is evident on the initial day of monitoring but not apparent
on subsequent days. Thus the typical solution is to discount the first day of monitoring entirely. Rodgers and Tudor-Locke (2006) outline that if monitoring occurs without feedback being provided on what is being observed (pedometer not providing the subject with step count data) will result in only a minimal or clinically insignificant degree of reactivity. They also outline that intervention studies, where there is an expectation that the subjects physical activity should increase for example may experience an increased Hawthorne effect which would not be observed in observational studies.

2.5.6 Seasonality and Weather Conditions
Seasonality and weather conditions have often been overlooked as determinants of physical activity. However, common knowledge as well as recently conducted literature dictates that both seasonality and weather conditions, such as amount of daylight, temperatures, and precipitation levels can majorly impact upon physical activity levels and behaviours, and thus must be considered when measuring physical activity. Poor weather has been identified as an environmental barrier to being physically active, with precipitation, cold weather and wind postulated as being the deterring factors to physical activity (Tucker and Gilliland 2007). It is important to note that although it rains during all seasons of the year, it is the continuous poor weather which acts as an ongoing deterrent to participation in physical activity. This is particularly relevant to walking outdoors, the common physical activity undertaken by all populations (Tucker and Gilliland 2007).

Seasonality is the systematic periodic increase or decrease in the prevalence or incidence of a health outcome or behaviour that corresponds to seasons or other calendar periods (McCormack et al. 2010).

The general consensus from the literature is that physical activity behaviours in the Northern Hemisphere are higher in summer than in winter (Newman et al. 2009, Buchowski et al. 2009, Pivarnik et al. 2003, Cheadle 2006) and a systematic review assessing the effect of season and weather on physical activity which included over 290,000 subjects found that levels of physical activity peaked in July and August and decreased in winter (Tucker and Gilliland 2007). In a study carried out on a UK population, which would have a similar climate to that of Ireland, Sumukadas et al. (2009) found day length, sunshine duration and maximum temperature all had a
significant \((p< 0.05)\) influence on physical activity levels. Furthermore the results showed a striking difference in the objectively measured daily activity in summer compared to winter, with the subjects enrolled in summer being twice as active as those enrolled in winter.

Therefore, the time of year in which measurements of habitual physical activity occurs as well as the weather conditions for a particular day must be taken into account when analysing physical activity levels.

### 2.6 Measurement Tools

Measurement of physical activity is important and there are numerous uses for its output (Bauman et al. 2006). Firstly, measurement allows for determination of whether national and international recommendations for physical activity are being met on an individual and population level. Furthermore, it is used in epidemiological research to assess the relationship between physical activity and a range of health outcomes. It is also used in the research domain to understand the correlates and determinants of physical activity and thus help to explain why differences in activity levels are visible in various populations. It is also used to monitor the effectiveness of interventions which are designed to increase physical activity. Overall, it is used to provide a sound and strong evidence base in order to dictate health policy and practice.

Thus, when evaluating physical activity it is important that measurement occurs accurately. However physical activity is inherently difficult to measure precisely, especially when individuals are undertaking everyday activities (Brage et al. 2005). The assessment of physical activity has been performed using a multitude of tools, both subjective and objective. To date, no tool has fulfilled the criteria of being valid, reliable, accurate and practical, while not affecting behaviour (Warms 2006). Each has both positives and negatives aspects to its use.

#### 2.6.1 Subjective Measures

Self-report measurement tools for physical activity are advantageous due to their low cost, applicability to large populations and overall practicality (Tudor-Locke and Myers 2001). However, such methods have many concurrent associated limitations.
Subjective measures of physical activity have been found to demonstrate only an overall low to moderate correlation (0.37) to objective measures of physical activity due to both over and underestimation of physical activity levels (Prince et al. 2008). Furthermore, it has been found that self-report methods are subject to a floor effect whereby they are not sensitive enough to detect the lowest levels of physical activity (Tudor-Locke and Myers 2001), indicating that subjective measures are unlikely to be sufficiently sensitive to capture light and moderate activities including household tasks and self-care tasks. Thus subjective measures are not suited to the measurement of physical activity in typically sedentary populations with low levels of physical activity (Tudor-Locke and Myers 2001). Furthermore, the validity of self-report methods relies on good cognitive status of the individual, which is not necessarily guaranteed in many clinical groups. Daily diaries, in particular are linked with poor compliance issues. They require the individual to record daily and the accuracy linked with this may prove to be a burdensome task for individuals. Paper diaries also tend to have a high level of “faked” compliance (Reiser and Schlenk 2009) and inaccurate recall also proves problematic with this method. Given the numerous limitations associated with the use of subjective self-report measures of physical activity, the research has turned preferentially to the objective methods of measuring physical activity.

2.6.2 Objective Measures
Coupling subjective physical activity measures with a form of objective measurement will enhance accuracy (Vanhees et al. 2005). Direct observation, pedometers, accelerometers, calorimetry (both direct and indirect) and the doubly labelled water method are all forms of objective measurement used to evaluate physical activity levels.

2.6.2.1 Direct Observation
Direct observation is the monitoring of physical activity behaviour through observation of the population under investigation. This is usually undertaken by trained observers. The main advantage of direct observation is that it allows for contextually rich data to be obtained in the form of the type of activity as well as when, where and with whom it occurs (Valanou et al. 2006). Furthermore, it also allows for estimation of energy expenditure, through use of the energy costs outlined
in the Compendium of Physical Activities (Ainsworth et al. 2000). However, there are also a number of limitations associated with it. Observations are confined to relatively short periods, thus not reflecting habitual activity. Furthermore, observation of an individual may result in the modification of their behaviour. The necessity for trained individuals to complete the observations, as well as the necessity for one observer for each subject being monitored means that the cost of conducting direct observation may be prohibitive.

2.6.2.2 Pedometers
Pedometers are devices that measure the number of steps taken through the use of motion sensing components. Pedometers are typically worn at waist level and respond to vertical acceleration of the hip during ambulatory activities. The accuracy of pedometer step recordings can be affected by an alteration in gait or placement issues. If the pedometer movement is restricted by clothing, body configuration or poor placement, the results will be affected. Limiting factors also include its inability to measure upper body activity or intensity of activity. However, the main advantages of pedometers relate to their low cost and unobtrusiveness and if walking activity is the outcome under investigation the pedometer can be a useful tool.

2.6.2.3 Accelerometers
Another available motion sensing device is an accelerometer. Accelerometers are devices that measure movement in up to three dimensions. Movement can be recorded using a range of transducers; the most common of which is in use in human movement applications being a piezoelectric sensor (Chen and Bassett Jr 2005). Despite the range of transducers in use, all use a similar system, which is a variation on the spring mass system, to measure acceleration (Mathie et al. 2004). This system works by means of when acceleration occurs, a small seismic mass within the accelerometer responds by applying a force to the piezoelectric element, causing it to deform in some way (stretch, bend, compress). This displacement can be measured and used to calculate the acceleration occurring (Mathie et al. 2004, Chen and Bassett Jr 2005). The raw accelerometry signal is filtered and amplified and then sampled to convert the signal to a series of numbers which are called “raw counts” or “activity count” (Chen and Bassett Jr 2005).
Accelerometers offer a number of desirable features in the monitoring of physical activity. Firstly they are superior to pedometers as they respond to both the frequency and intensity of movement. Measuring acceleration (which is the change in speed with respect to time); more accurately allows intensity of activity to be recorded. Secondly, many can be used to measure tilt, thus allowing them to measure components of physical activity behaviour.

Accelerometers, however, are much more expensive in comparison to pedometers and self report measures especially when the cost of equipment used in the programming and data analysis are factored into the cost. This is even despite the advances in the technology relating to microelectromechanical systems, which has reduced the cost somewhat. The increased sensitivity of accelerometers unfortunately means that it may be sensitive to vibrational artefact and can record background vibration, such as being in a vehicle, incorrectly as movement.

Another major issue regarding this tool is that the unit of measurement (raw or activity count) produced by the equipment is not standardised and no direct translation to meaningful data exists. Instead, each individual accelerometer manufacturer produces programs based on complex algorithms to calculate meaningful data.

2.6.2.4 Doubly Labelled Water
Doubly labelled water (DLW) is considered to be the “gold standard” criterion for measuring energy expenditure in free-living situations (Melanson and Freedson 1996). The principle of DLW is to ingest a standardized amount of two stable isotopes (Hydrogen (H) and Oxygen (O)) as water (H\textsubscript{2}O). The difference in elimination rates (over 5-14 days) of the isotopes provides a measure of the CO\textsubscript{2} (carbon dioxide) production and therefore energy expenditure (Schoeller 1999, Schoeller 2007, Vanhees et al. 2005). However, limitations related to the DLW method exist and include the high financial cost, the need for trained personnel to perform the technique and the fact that the method can only be used to measure energy expenditure over a long period of time (10-14 days) (Andre and Wolf 2007).
2.6.2.5 Calorimetry
Calorimetry is also considered a criterion method of measuring energy expenditure (Vanhees et al. 2005). Direct calorimetry involves the measurement of energy expended based upon measurement of heat emitted by the body (Montoye et al. 1996). Indirect calorimetry estimates total energy expenditure from O2 (oxygen) consumption and CO2 production (Matarese 1997, Battley 1995, Valanou et al. 2006). However, the equipment used in calorimetry measurements limit its use in free-living situations.

2.6.2.6 Multi-location accelerometers
Multi-location accelerometers are one of the emerging technologies in the area of physical activity measurement. These tools involve the measurement of the acceleration at two or more body segments. This has generally been conducted in small scale pilot type studies in the laboratory setting (Chen and Bassett Jr 2005). However, one such monitor has been developed and is commercially available. The Intelligent Device for Energy Expenditure and Activity (IDEEA) utilises accelerometry signals from five sites (mid-thigh and feet bilaterally and chest), is small and portable and is capable of recording up to seven days continuous data. The benefit of these monitors relates to their ability to monitor postural changes and slow motions superiorly than the traditional single site accelerometer.

2.6.2.7 Multi-sensor devices
Multi-sensor devices are another of the emerging technologies in this area. These devices are a combination of accelerometry with other physiological variables in a single unit device. The integration of movement data from accelerometers and physiological data is proposed to provide a more in depth, robust and accurate measure of energy expenditure (Lamonte and Ainsworth 2001). The most well researched commercially available multi-sensor monitors are the ActiHeart (combines heart rate and inter-beat interval with accelerometry) and the SenseWear Armband (combines skin temperature, galvanic skin response, heat flux, and near-body temperature with accelerometry).

2.6.2.7.1 SWA
The SenseWear (SWA) is a multi-sensor physical activity monitor manufactured by Bodymedia (Bodymedia Inc., Pittsburgh, PA, USA). The SWA continuously records
an array of physiological data from the four sensors contained on the armband (skin temperature, galvanic skin response, heat flux, and near-body temperature) as well as by accelerometry (Liden et al. 2002). Accelerometry is measured using a two-axis accelerometer. Heat flux is measured using a propriety sensor which incorporates low thermal resistant materials and thermocouple arrays. Galvanic skin response is measured by two hypoallergenic stainless steel electrodes and assesses the degree of evaporative heat loss. Skin temperature is used to account for the body’s core temperature and is measured using a thermistor-based sensor. The near-body temperature sensor measures the temperature at the outer edge of the heat flow sensor (Liden et al. 2002). Data from these sensors are combined with gender, age body weight, height, handedness and smoking status data, using proprietary algorithms developed by the manufacturers. SWA has been validated to measure energy expenditure in the normative population (Berntsen et al. 2010, Johannsen et al. 2010, Jakicic et al. 2004, St-Onge et al. 2007) and more recently by ourselves in the RA population (Chapter 5).

2.7 CONCLUSION

This chapter has endeavoured to provide insight into the condition of Rheumatoid Arthritis in terms of its symptoms, epidemiology and the related concept of Rheumatoid Cachexia.

It has also sought to enlighten the reader with regard to the concept of physical activity. In particular, the chapter has outlined what the term encompasses, the differing “proxy measures” of physical activity, in particular step count and energy expenditure and how physical activity is measured.

This chapter seeks to provide the reader with background information on both Rheumatoid Arthritis and physical activity, which are two concepts which will be detailed further in later chapters.
**SECTION 1:**

This section of the thesis encompasses Chapter 3, 4 and 5, three pieces of work which have been published or accepted for publication and set up the motivation for the exploratory studies outlined further in this thesis.

Chapter 3 will outline that a lack of clarity regarding the physical activity levels of the RA population exists, largely attributable to methodological shortcomings noted in the protocols of previously conducted research in this area, particularly the use of subjective physical activity measurement tools or tools which have not been validated for use in the RA population.

Chapter 4 will highlight the increased inflammation related cardiovascular mortality risk in the RA population and the links between physical activity levels and inflammation related cardiovascular disease in other populations. The lack of research conducted in this area in the RA population will also be highlighted.

Chapter 5 was developed with the intention of rectification of one of the methodological shortcomings noted in Chapter 3. This chapter will outline the results of a study which validated the energy expenditure output of the objective physical activity measurement tool, the SWA for use in the RA population, thereby inspiring confidence in the physical activity output of studies utilising this tool.
CHAPTER 3 PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

3.1 INTRODUCTION
As previously outlined, in healthy individuals, basal and resting metabolic rates account for approximately 65% of daily energy expenditure. The thermic response to food (absorption, digestion, transport and storage) account for about 10% and the remaining 25% of total daily energy expenditure is accounted for by physical activity (Levine 2007).

However, resting energy expenditure (REE), which is the amount of calories required by the body during a non active period, can be significantly altered by a number of factors including chronic inflammatory disease (Metsios et al. 2008a, Roubenoff et al. 2002). Rheumatoid cachexia, is a significant concurrent problem within this population group (affecting approximately two thirds of individuals) and the overproduction of tumor necrosis factor-α (TNF-α) associated with this cachexic state has been shown to increase REE (Roubenoff et al. 1994). For this reason, the proportion of total energy expenditure (TEE) attributed to physical activity is reduced in this population.

It is generally assumed that daily physical activity is also reduced in patients with RA as a result of joint pain, restricted mobility, fatigue, reduced muscle mass, strength and endurance (Roubenoff 2009, Plasqui 2008). However, there is little research available assessing free living physical activity levels in individuals with RA or comparing the levels between those with RA and healthy controls.

Thus, a systematic review was conducted to examine the levels of physical activity among individuals with RA.

3.2 METHODOLOGY
A systematic review was conducted by one of the authors (MT) to identify all published literature relating to the measurement and reporting of levels of physical activity and/or energy expenditure in people with RA.

Based on the recommendations of the Cochrane handbook for systematic reviews (Higgins and Green 2009), the databases Embase and MEDLINE were searched for
relevant texts. AMED, Biomedical Reference Collection Expanded, CINAHL, Nursing and Allied Health Collection and SportsDiscus were also searched.

The search strategy involved combining two sets of keywords:

For Embase, EMTREE terms were used. In this case the search consisted of:

rheumatoid arthritis AND leisure OR energy expenditure OR physical activity

For MEDLINE, MeSH terms were used. In this case the search consisted of:

Arthritis, Rheumatoid AND Leisure Activities OR Motor Activity OR Energy Metabolism

For the other EBSCO databases searched, the search strategy consisted of the use of the following terms in the subject terms:

Rheumatoid Arthritis AND Leisure activit* OR physical activit* OR energy expendit*, where * indicates the wildcard character and denotes the use of all possible suffixes.

The results included all publications published up to Jan 31st 2011 that included at least one search term from each of the two categories. The search was extended by secondary searching of the reference lists of papers retrieved to identify any additional references for recovery. Only English language publications were included.

The electronic searches identified 136 studies. The titles of all identified articles were examined for relevance. If it was not clear from the title if the study was relevant, the abstract was also examined. To be included in the review, studies had to 1) measure and report on free living physical activity levels or total/activity related energy expenditure levels for at least 24 hours, 2) be related to the RA population with all subjects included in studies fulfilling the criteria set down by the American College of Rheumatology, 1987 (Arnett et al. 1988) and 3) be related to the adult population. Studies which were 1) interventional in nature with the objective of increasing the levels of physical activity 2) not designed with purpose of collecting new data or 3) not published in full text format were not included.
As demonstrated by the flowchart (Fig. 3.1), 106 of the publications examined were excluded as they clearly not relevant based on article title and/or abstract. Thirty papers were retrieved in full text for further analysis as based upon the information provided in the title and/or abstract, the articles potentially met the inclusion criteria. After inspection of the full texts, 14 publications were excluded leaving 16 publications deemed suitable for inclusion in this review.

**FIGURE 3.1 FLOW CHART OUTLINING METHODOLOGY**

136 studies identified through electronic searching

106 excluded based on title ± abstract

- 85 did not report on free living physical activity/energy expenditure levels
- 20 not suitable due to study design
- 1 related to paediatric population

30 retrieved in full text

14 excluded based on full text analysis

- 10 did not report on free living physical activity/energy expenditure levels
- 3 did not fulfil ACR criteria for diagnosis of RA
- 1 not suitable due to study design

16 included in systematic review
As no randomised controlled trials were included in this review, a system to appraise non-randomised studies had to be applied. The system which was applied was based on the Newcastle-Ottawa Quality Assessment Scale (Wells), with some modifications made to best serve the nature of the articles assessed, similar to that proposed by Smedslund and Birger Hagen (2010). As referred to by Juni et al. (1999), the incorporation of quality scores lacks statistical or empirical justification and for this reason scores of “met”, “unclear” and “not met” were used. The quality of the studies was assessed by one of the authors (MT) and another researcher uninvolved in the development of the review. Any disagreements in findings between the two reviewers were resolved by consensus. Inter-reviewer disagreements centred on the representativeness aspect of the scale. The assessment tool used is outlined in Appendix B.

3.3 RESULTS

A total of 16 studies published between 2001 and 2011 that examined free living physical activity in RA were included in this review. The majority of the studies were cross-sectional in nature (n=15) with one utilising a cohort study design.

A total of 1890 RA subjects (range 12-298) were included in this review. Descriptive characteristics of these participants are presented in Table 3.1.
<table>
<thead>
<tr>
<th>Author, Year, Location</th>
<th>Study Design</th>
<th>Subjects/ Controls (N)</th>
<th>RA participants Age (years)</th>
<th>Sex ratio Female: Male</th>
<th>Disease Activity</th>
<th>Disease Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemmey et al. (2001), United Kingdom</td>
<td>Cross-Sectional</td>
<td>73/82</td>
<td>52.9 ± 12.9 (mean ± SD)</td>
<td>46:27</td>
<td>Not reported on</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Roubenoff et al. (2002), USA</td>
<td>Cross-Sectional</td>
<td>20/20</td>
<td>47 ± 14 (mean ± SD)</td>
<td>All female</td>
<td>Not reported on</td>
<td>92.4 ± 78 (mean ± SD)</td>
</tr>
<tr>
<td>Semanik et al. (2004), USA</td>
<td>Cross-Sectional</td>
<td>185/0</td>
<td>70 (60 – 88) (mean (range))</td>
<td>All female</td>
<td>Not reported on</td>
<td>211.2 (7.2 – 792), 151.2 (average (range), SD)</td>
</tr>
<tr>
<td>Eurenius and Stenstrom (2005), Sweden</td>
<td>Cross-Sectional</td>
<td>298/0</td>
<td>57 (19-90) (median (range))</td>
<td>225:73</td>
<td>Not reported on</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Hagfors et al. 2005,</td>
<td>Cross-Sectional</td>
<td>32/0</td>
<td>Not reported on</td>
<td>29 : 4 (of 33 initially included)</td>
<td>Not reported on</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Greene et al 2006, USA</td>
<td>Cross-Sectional</td>
<td>52/30</td>
<td>61.0 ± 14.5 (mean ± SD)</td>
<td>47 : 5</td>
<td>Not reported on</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Wikstrom et al. (2006), Sweden</td>
<td>Cross-Sectional</td>
<td>144/144</td>
<td>60.4 ± 13.3 (mean ± SD)</td>
<td>111 : 33</td>
<td>4.61 ± 1.31 mean ± SD (DAS-28)</td>
<td>7.5 ± 2.8 (mean ± SD)</td>
</tr>
<tr>
<td>Eurenius et al. (2007), Sweden</td>
<td>Cross-sectional</td>
<td>98/0</td>
<td>57 (19 – 84) (median (range)) based on 102 initially included</td>
<td>72 : 26</td>
<td>Not reported on</td>
<td>15 (4 -78) (median (range)) based on 102 initially included</td>
</tr>
<tr>
<td>Mancuso et al. (2007), USA</td>
<td>Cross-Sectional</td>
<td>121/120</td>
<td>49 (19 – 72) (mean (range))</td>
<td>102 : 19</td>
<td>Not reported on</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size</td>
<td>Sex</td>
<td>Age Mean ± SD</td>
<td>Gender Specific Age Median ± IRQ</td>
<td>Disease Activity Score Mean ± SD</td>
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<tr>
<td>Van den Berg et al. (2007), Netherlands</td>
<td>Cross-Sectional</td>
<td>252/0</td>
<td>Not reported on</td>
<td>165 :87</td>
<td>Not reported on</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Tourinho et al. (2008), Brazil</td>
<td>Cohort</td>
<td>71/29</td>
<td>All female</td>
<td>38.1 ± 6.62 (mean ± SD)</td>
<td>All female</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Raftery et al. (2009), United Kingdom</td>
<td>Cross-Sectional</td>
<td>12/12</td>
<td>All female</td>
<td>Not reported on</td>
<td>All female</td>
<td>Not reported on</td>
</tr>
<tr>
<td>Stavropoulos – Kalinoglou et al. (2009), United Kingdom</td>
<td>Cross-Sectional</td>
<td>150/0</td>
<td>Males: 60 (59-64) Females: 59 (55-64) (median (IRQ))</td>
<td>102 : 48</td>
<td>Males 4.4 (2.6 – 5.3) Females 3.8 (2.9 – 5.1) median (IRQ) (DAS-28)</td>
<td>Males: 84 (48-144) Females: 108 (60-168) (median (IRQ))</td>
</tr>
<tr>
<td>Hurkmans et al. (2010), Netherlands</td>
<td>Cross-Sectional</td>
<td>271/0</td>
<td>All female</td>
<td>62 ± 14 (mean ± SD)</td>
<td>178 : 93</td>
<td>3.5 ± 4.6 mean ± SD (RADAI)</td>
</tr>
<tr>
<td>Piva et al. (2010), USA</td>
<td>Cross-Sectional</td>
<td>47/0</td>
<td>All female</td>
<td>56.5 ± 7 (mean ± SD)</td>
<td>All female</td>
<td>3.0 ± 0.81 mean ± SD</td>
</tr>
<tr>
<td>Elkan et al. (2011), Sweden</td>
<td>Cross-Sectional</td>
<td>61/0</td>
<td>All female</td>
<td>60.8 (57.3 – 64.4) (mean (CI))</td>
<td>All female</td>
<td>3.3 (3.0 – 3.6) mean (CI)</td>
</tr>
</tbody>
</table>

Table 3.2 outlines details regarding the methodology of the included studies as well as the main pertinent findings.
<table>
<thead>
<tr>
<th>Author, Year, Location</th>
<th>Inclusion Criteria for subjects</th>
<th>Measurement Tool</th>
<th>Variable recorded</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemmey et al. (2001), United Kingdom</td>
<td>Met ACR criteria for RA Adult population</td>
<td>8 point physical activity scale</td>
<td>Exercise level</td>
<td>RA participants had exercise level of 0.8 ± 0.7 SD Non RA rheumatic participants had exercise level of 0.7 ± 0.1 SD Age and sex matched healthy controls had exercise level of 5.4 ± 1.7 SD</td>
</tr>
<tr>
<td>Roubenoff et al. (2002), USA</td>
<td>Met ACR criteria for diagnosis of RA Stable drug regimen Free of disease flare up for ≥ 3months before entry to study</td>
<td>DLW Caltrac accelerometer Paffenbarger Physical Activity and Exercise Index</td>
<td>kJ/day kJ/day kJ/day</td>
<td>DLW: RA patients 2,849 ± 1,075 kJ/day, Controls: 3,883 ± 1,732 kJ/day Caltrac accelerometer: RA patients 1,264 ± 992 kJ/day, Controls: 2,280 ± 1,469 kJ/day Paffenbarger questionnaire: RA patients 2,188 ± 1,397 kJ/day, Controls: 3,150 ± 1,611 kJ/day</td>
</tr>
<tr>
<td>Semanik et al. (2004), USA</td>
<td>English speaking Aged ≥ 60 years Cognitively intact Women Able to walk household distances Diagnosed by a board-certified rheumatologist as having RA according to ACR 1987 revised criteria</td>
<td>Yale Physical Activity Survey (YPAS)</td>
<td>Hours per week and mins per day spent in selected physical activities by intensity</td>
<td>Low intensity (&lt;3.0 METs): 68.0 mean minutes/day Moderate intensity (3.0-5.5 METs): 117.0 mean minutes/day High intensity (≥6.0 METs): 12.9 mean minutes/day 10 hours less per week in physical activity than community dwelling elderly women with musculoskeletal impairments</td>
</tr>
<tr>
<td>Study</td>
<td>Region</td>
<td>Study Details</td>
<td>Methodology</td>
<td>Physical Activity Details</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Eurenius and Stenstrom (2005), Sweden</td>
<td>Confirmed diagnosis of RA</td>
<td>Disease duration ≤ 6.5 years</td>
<td>Specially designed self report questionnaire</td>
<td>Sum score for self report physical activity questionnaire</td>
</tr>
<tr>
<td>Hagfors et al. 2005,</td>
<td>RA according to American College of Rheumatology criteria</td>
<td>3-day Activity Register (AR) (32 subjects)</td>
<td>Total Energy Expenditure (TEE) (MJ/day)</td>
<td>TEE via AR: 9.29 ± 1.27 MJ/day TEE via DLW: 10.76 ± 2.59</td>
</tr>
<tr>
<td>Greene et al. 2006, USA</td>
<td>Older than 30 years of age</td>
<td>Physical Activity and Disability Survey (PADS)</td>
<td>Time spent lying down (hr/day)</td>
<td>RA individuals: Lying down: 5.6 ± 3.4 Exercise: 22.4 ± 37.4 Leisure: 1.5 ± 2.3 Household: 1.5 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Classified as having RA according to American College of Rheumatology criteria</td>
<td>Exercise time (min/day)</td>
<td>Leisure Activity Time (hr/day)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reported less than 1 hour of morning stiffness</td>
<td>Leisure: 1.5 ± 2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Comprehended English</td>
<td>Household Activity Time (hr/day)</td>
<td>Total Physical Activity Time (hr/day)</td>
<td>Total Physical Activity: 3.4 ± 3.0</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------</td>
<td>---------------------------------</td>
<td>--------------------------------------</td>
<td>----------------------------------</td>
</tr>
</tbody>
</table>
| Wikstrom et al. (2006), Sweden | Diagnosis of RA according to ACR revised 1987 criteria  
Disease duration of 1 year or less | Leisure Activity Scale | Interest, performance, importance and change due to illness in leisure activity domains | Subjects performed in fewer leisure activity domains (8.2 ± 3.1) compared to controls (9.9 ± 2.6). |
| Eurenius et al. (2007), Sweden | Confirmed diagnosis of RA  
Disease duration ≤ 6.5 years  
Included on Swedish RA register  
Had to be able to perform at least 3 of 5 tests of bodily function and complete 1 of 2 questionnaires | Specially designed self report questionnaire | Sum score for self report physical activity questionnaire | 36% of subjects did not meet recommendations on healthy physical activity behaviours  
Median physical activity score at baseline was 14 (range 5 – 30). At 1 year follow up, no statistically significant changes were found; with a median physical activity score of 13.25 (range 1 – 27.5). |
| Mancuso et al. (2007), USA | 18 years of age or older  
Fluent in English or Spanish  
Met ACR 1987 revised criteria for RA  
Currently employed for salary | Paffenbarger Physical Activity and Exercise Index | kcals/week | RA patients 1,474 ± 1,198 kcals/week.  
Controls 1,958 ± 1,940 kcals/week (mean ± SD)  
At 1 year follow up: RA patients 1,459 ± 1,368 kcals/week. Controls 1,928 ± 1,501 kcals/week (mean ± SD)  
Subjects expended statistically significantly less kcals/week than controls |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>RA Diagnosis (1987 revised ACR criteria)</th>
<th>Physical Activity Measure</th>
<th>Minutes/Week Meeting National Recommendations</th>
<th>RA Population Compared to General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Berg et al. (2007), Netherlands</td>
<td>Netherlands</td>
<td>Rheumatologist confirmed diagnosis of RA according to 1987 ACR criteria</td>
<td>Short Questionnaire to ASsess Health (SQUASH) – Enhancing physical activity</td>
<td>Mins/week</td>
<td>RA population reported significantly less minutes of physical activity per week than the general population – RA patients: 1,535 min/week, general population: 1,869 min/week. Similar results were obtained for the RA and general populations regarding meeting public health recommendations.</td>
</tr>
<tr>
<td>Tourinho et al. (2008), Brazil</td>
<td>Brazil</td>
<td>Pre-menopausal women Fulfilled the criteria for RA, according to the American College of Rheumatology Not in situations previously defined as determents of bone loss or increase</td>
<td>Specific questionary to individuals about physical activity they usually do</td>
<td>% in different physical activity categories</td>
<td>Sedentarism: 17.3% Mild physical activity: 57.7% Moderate physical activity: 25% Intense physical activity 0% Women with RA were statistically significantly more likely to be sedentary (p=0.044) and less likely to be moderately active (p=0.004) than healthy women.</td>
</tr>
<tr>
<td>Raftery et al. (2009), United Kingdom</td>
<td>United Kingdom</td>
<td>Fulfilled the American College of Rheumatology (ACR) criteria for RA No other disabling conditions</td>
<td>Numact activity monitor</td>
<td>Total energy (arbitrary units) Number of steps taken Vigor of steps Time spent standing (secs)</td>
<td>Mean total energy: RA: 298 units; FM: 307 units Mean total number of steps: RA: 9,916; FM: 11,397 Mean vigor of steps: RA: 28.2; FM: 26.6 Mean time standing: RA: 15,949 secs; FM: 15,549 secs</td>
</tr>
<tr>
<td>Stavropoulos – Kalinoglou et al. (2009), United Kingdom</td>
<td>United Kingdom</td>
<td>RA diagnosis (1987 revised ACR (American College of Rheumatology) criteria)</td>
<td>IPAQ</td>
<td>METmin per week</td>
<td>Males: 2,607 (2,179 – 3,412) METmin per week</td>
</tr>
<tr>
<td>Kingdom</td>
<td>Diagnosis of RA according to the criteria of the American College of Rheumatology</td>
<td>Short QUestionnarie to ASsess Health (SQUASH) – Enhancing physical activity</td>
<td>Mins / week</td>
<td>Patients with RA were physically active for an average of 1,717 mins per week</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Hurkmans et al. (2010), Netherlands</td>
<td>Diagnosis of RA according with the American College of Rheumatology criteria</td>
<td>SenseWear Professional v 6.1 Armband</td>
<td>kcals/day</td>
<td>Participants expended an average of 199 kcals/day at moderate intensity activity (3METS and above)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis for at least 2 years</td>
<td>Daily average number of steps</td>
<td></td>
<td>Participants expended an average of 7,151 steps</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No cardiovascular events prior to recruitment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piva et al. (2010), USA</td>
<td>RA diagnosis in conjunction with ACR criteria</td>
<td>Short self-administered version of IPAQ</td>
<td>MET-hours/day</td>
<td>The total physical activity level was 40.00 (37.4-44.7) (median (IQR)) MET-hours/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease duration ≥ 1 year</td>
<td></td>
<td></td>
<td>This corresponds to the activity of healthy Swedish women of same age. However, physical activity measurement was not conducted in similar manner in both studies.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Could not have: current malignancy, severe heart failure, severe renal failure, chronic obstructive lung disease with emphysema, earlier gastric ulcer or intestinal surgery or known eating disorder</td>
<td></td>
<td></td>
<td>In 21% of the RA population, physical activity levels were considered low.</td>
<td></td>
</tr>
</tbody>
</table>
The quality of the studies included in this review based on the modified Newcastle Ottawa Scale are outlined in Table 3.3.

### TABLE 3.3 QUALITY OF STUDIES INCLUDED IN REVIEW

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemmey et al. 2001</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>Met</td>
</tr>
<tr>
<td>Roubenoff et al. 2002</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>Met</td>
</tr>
<tr>
<td>Semanik et al. 2004</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Eurenius and Stenstrom 2005</td>
<td>Not met</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hagfors et al 2005</td>
<td>Not met</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Greene et al. 2006</td>
<td>Not met</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>Met</td>
</tr>
<tr>
<td>Wikstrom et al. 2006</td>
<td>Met</td>
<td>Met</td>
<td>Not met</td>
<td>Unclear</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
</tr>
<tr>
<td>Eurenius et al. 2007</td>
<td>Not met</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
</tr>
<tr>
<td>Mancuso et al. 2007</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
</tr>
<tr>
<td>van den Berg et al. 2007</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tourinho et al. 2008</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Unclear</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
</tr>
<tr>
<td>Raftery et al. 2009</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Not met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
</tr>
<tr>
<td>Hurkmans et al. 2010</td>
<td>Met</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Piva et al. 2010</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Stavropoulos-Kalinoglou et al. 2010</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Elkan et al. 2011</td>
<td>Unclear</td>
<td>Met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>Met</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Key:

1: Representativeness  
2: Ascertainment of exposure  
3: Subjects blinded to study aims  
4: Duration covering full range of variation  
5: Diagnosis  
6: Adequate use of statistics  
7: Attrition  
8: Comparability  

N/A: not assessed
Due to the nature of the assessment scale, it is inappropriate to apply quality scores. However, no study achieved fulfilment of all of the quality criteria. Blinding of subjects was not achieved by any of the studies included, although the authors of this review acknowledge the difficulties of blinding in non-randomised studies. A number of studies (N=9) did not utilise a control group. Of those which did six out of seven (Lemmey et al. 2001, Roubenoff et al. 2002, Wikstrom et al. 2006, Tourinho et al. 2008, Mancuso et al. 2007, Greene et al. 2006) successfully matched groups for age and gender. The exception was the study conducted by Raftery et al. (2009), in which it is unclear. Greene et al. (2006) and Raftery et al. (2009) used patient populations as controls and Lemmey et al. (2001) used both patient and healthy population controls whilst the remainder used solely healthy populations. Three (Wikstrom et al. 2006, Eurenius et al. 2007, Tourinho et al. 2008) of the four studies which completed a follow up of subjects, were able to complete follow up of all subjects or maintain numbers lost to less than 20%. In addition, only two studies (Wikstrom et al. 2006, Hurkmans et al. 2010) clearly demonstrated that the sample included was truly representative of the average patient with RA. All studies included in this review ensured that participants had a formal diagnosis of rheumatoid arthritis according to the American College of Rheumatology (ACR) criteria (Arnett et al. 1988) and this was included as an aspect of their inclusion criteria. Although a misprint indicates that this may not be the case in the studies conducted by Eurenius and Stenstrom (2005) and Eurenius et al. (2007), correspondence with the authors verify that all patients included have a diagnosis in accordance with ACR criteria.

Four of the studies (Roubenoff et al. 2002, Raftery et al. 2009, Hagfors et al. 2005, Piva et al. 2010) in the review utilised objective measurement tools while the remaining 12 used only subjective outcome measures. The use of differing measurement tools leads to greatly differing output styles also. They include kJ/day (Roubenoff et al. 2002), hrs/week (Semanik et al. 2004), hrs/day (Greene et al. 2006), mins/day (Semanik et al. 2004, Greene et al. 2006), MJ/day (Hagfors et al. 2005), kcals/week (Mancuso et al. 2007), mins/week (van den Berg et al. 2007, Hurkmans et al. 2010), kcals/day (Piva et al. 2010), METmin per week (Stavropoulos-Kalinoglou et al. 2010) and METhours/day (Elkan et al. 2011), as well
as exercise level (Lemmey et al. 2001), physical activity level (Hagfors et al. 2005), sum score of outcome measure (Eurenius et al. 2007, Eurenius and Stenstrom 2005), meeting of national recommendations (van den Berg et al. 2007), daily average number of steps (Piva et al. 2010), number of steps taken (Raftery et al. 2009), vigor of steps (Raftery et al. 2009), time spent standing (Raftery et al. 2009), total energy in arbitrary units (Raftery et al. 2009), participation in activity domains (Wikstrom et al. 2006) and % in different physical activity categories (Tourinho et al. 2008).

3.4 Discussion

The results of this systematic review indicate that physical activity levels among the RA population may be decreased when compared to healthy controls and is lower than the current international recommendations outlined to maintain a healthy lifestyle.

There are a number of methodological considerations at play in the studies reviewed which prohibits us from conclusively defining the physical activity levels of this population group, and thereby definitively stating that the physical activity levels of this population are decreased.

3.4.1 Measurement Tools

The measurement tools and consequently output styles used varied greatly in each of the studies reviewed, from objective measures and output styles to subjective measures and output styles, with or without validation specific to this population group. Although some of these findings can be converted to allow for comparison, some, in particular some of those reported by subjective measures do not lend themselves to conversion, making accurate comparison difficult. Furthermore, some of the tools measured TEE (thereby encompassing more than physical activity) while some only examined specific aspects of certain physical activities. Therefore, efforts to compare what is measured by each are hampered further.

The decision of which measurement tool to accurately account for physical activity levels or energy expenditure levels has been the cause of debate (Ward et al. 2005). Subjective methods are generally not as expensive and are easier to administer than objective measures of physical activity. However, they are also subject to numerous
disadvantages including misrepresentation, misinterpretation, accuracy in recall, and intensive effort and motivation on the part of the subject (Valanou et al. 2006). Prince et al. (2008) assessed the comparison of direct versus self report measures for assessing physical activity in adults using a range of subjective and objective measures and found a generally low to moderate correlation between the two methods. The Doubly Labelled Water (DLW) method is the gold standard criterion for measuring energy expenditure and gives most accurate information (Plasqui and Westerterp 2007, Hoos et al. 2003). However, due to the high cost of isotopes, the cost and complexity of analysis with gas isotope-ratio mass spectroscopy, there is limited applicability of the DLW method in large population studies (Valanou et al. 2006).

The ideal method of physical activity measurement should be accurate, precise, objective, simple to use, robust, time efficient, cause minimal intrusion into habitual activity patterns, be socially acceptable, allow for continuous and detailed recording of usual activity patterns, and finally, should be applicable to large population groups (Livingstone et al. 2003). When working with a clinical population, particularly a condition like RA where joint involvement is a feature of the disease, ease of use must be a major consideration. This is highlighted by the high percentage of RA patients necessitating the use of aids, appliances and assistive devices in activities of their daily living (Kennedy et al. 2007, de Boer et al. 2009).

3.4.2 TERMINOLOGY
By definition, physical activity is ‘any bodily movement produced by skeletal muscles that results in energy expenditure’ whereas ‘exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness’ (Caspersen et al. 1985). However, Lemmey et al. (2001) used both the terms ‘exercise’ and ‘physical activity’ interchangeably within the text. This makes it difficult to compare the findings of this study with normative data and also with other studies which have assessed physical activity or exercise in a RA population. However, this is the oldest of the studies included in this systematic review and it must be noted that authors of more recent texts appear more aware of the differences between the two terms when reporting the findings of their studies.
3.4.3 Comparison to National Guidelines

Eurenius and Stenstrom (2005), Eurenius et al. (2007), Mancuso et al. (2007) and van den Berg et al. (2007) indicated that the majority of the RA population which they assessed, although not as active as their normative comparisons, met the national guidelines for physical activity. Each of the studies gave overall time in activity values. The American College of Sports Medicine (ACSM) recommendation is for the accumulation of 30 minutes of moderate-intensity lifestyle physical activity in short segments (ten minute bouts) on most, if not all, days of the week (Haskell et al. 2007). Furthermore, the ACR also supports these recommendations for people with RA (Krebs 2003). However, none of the studies took into account the recommendation of the activity to be of minimum ten minute bout in duration, thereby assessing if the ACSM guidelines were met.

In a recent study conducted by Esliger et al. (2005), seven consecutive days of accelerometry measurements were gathered from a group of 94 adolescents. The results of minute by minute or cumulative physical activity monitoring indicated that 100% of the subjects were averaging ≥ 30 minutes moderate to vigorous physical activity (MVPA) per day, with 98% averaging ≥ 60 minutes MVPA daily. In comparison when the data was analysed to include bouts of MVPA ≥ 10 minutes continuously, only 6% achieved ≥ 30 minutes MVPA daily and only 2% achieved ≥ 60 minutes MVPA per day. These findings indicate the importance of being stringent in the measurement of ten minute bouts of activity rather than minute by minute activity, when aiming to determine whether ACSM guidelines have been reached.

The results highlighted in this review indicate that physical activity may be reduced in this population. These findings are based across an international spectrum and using a variety of physical activity outcome measures, both subjective and objective in nature. However, as highlighted by the quality assessment (Table 3.3) methodological flaws exist in each of the studies reviewed. For this reason, the validity of the evidence is questionable and an overall conclusion cannot be made.
3.5 Recommendations for Future Research

- Use of objective measurement tools in the assessment of free living physical activity in this population.
- Larger sample sizes when measuring with objective measures and sample size calculations. This will allow the results of the study to be reported with confidence.
- Subject data should be compared with controls, if possible patient controls. The use of controlled data as opposed to normative data ensures that the data from both groups will have been gathered in an identical manner and therefore differences can be reported on with confidence. Furthermore, it has been shown that patients with one disease may be undertreated for other diseases (Redelmeier et al. 1998, Brown et al. 2004) so it is important that both groups be drawn from patient population groups. However, it is likely that the use of control data from other rheumatology populations will not find large changes, as both groups will have large degrees of disability. The use of control data from non-disabled disabled populations will likely to be most representative of the differences in physical activity levels in the RA population compared to their peers.
- Use of outcome measures that have been proven valid and reliable in both the RA population and also for control populations.
- Physical activity monitoring of moderate intensity of ten minute bouts. There is evidence that lifestyle physical activity needs to be continuous ten minute bouts of self selected moderate intensity activity to provide cardiovascular and other health benefits (Haskell et al. 2007).
- The definitions of “physical activity” and “exercise” as described by Caspersen et al. (1985) should be strictly implemented as defined. This will ensure that study findings are more easily comparable.
- Use of easily modifiable output styles from outcome measures. This will also assist in ensuring that findings from various studies are more easily comparable.

3.6 Limitation

According to the Cochrane handbook for systematic reviews (Higgins and Green 2009), a systematic review should be undertaken by more than one person, to increase the likelihood that errors are detected. However, while the authors attempted to follow the Cochrane approach to systematic review methodology, unfortunately it was not feasible in all aspects of the methodology and in this review it was only possible to have two reviewers assess the quality of the studies.
3.7 Conclusion

This systematic review reports on the levels of physical activity in the RA population and outlines the differences between this population and national recommendations and both healthy and other rheumatology patient control populations.

The findings of this systematic review indicates that physical activity levels among individuals with RA may lower than those recommended and also when compared to healthy controls. This finding occurs irrespective of the measurement tool utilised.

However, although the findings appear to indicate this, this cannot be reported with certainty due to the limitations of measurement and as we have reported, many recommendations for future research which have not been applied in the studies carried out on this topic to date.

This review identifies the variability in physical activity measurement and lack of objective measurement of physical activity in RA and describes evidence that clearly supports the necessity of objective monitoring of physical activity levels within this population.

In addition, the reporting of physical activity levels in total volume values as well as moderate intensity levels that occur in ten minute bouts may allow greater comparability with specific regard to health benefits induced by physical activity (Haskell et al. 2007).

Furthermore the necessity of intervention to improve the physical activity levels within the RA population appears evident on the basis of the findings of this review. Individuals with RA are at an excessive cardiovascular disease risk compared to the general population (Solomon et al. 2003, Del Rincón et al. 2001), and therefore fostering appropriate physical activity appears fundamental and should be a priority to improve mortality rates in this population.
4.1 **INTRODUCTION**

As previously outlined, individuals with RA have increased mortality (approximately a 50% increase) compared to the general population (Aviña-Zubieta et al. 2008) with a greater than two fold higher risk of myocardial infarction (Solomon et al. 2003) and an almost four times higher number of cardiovascular events (Incidence rate ratio of 3.96) (Del Rincón et al. 2001). A number of reasons are postulated to explain why the greater risk occurs. Traditional cardiovascular risk factors, side effects of some drug treatments and non-traditional cardiovascular risk factors (including inflammation) have been deemed to be contributory, and inflammation has been deemed a key factor (Peters et al. 2010).

Regular physical activity is associated with improvements in health in many populations and in particular improvements in cardiovascular health, which is of distinct importance in this population group. Recently conducted studies of physical activity have consistently documented a decreased incidence of cardiovascular disease (CVD) in more physically active subjects in a graded manner (Aadahl et al. 2009, McGuire et al. 2009, Valle et al. 2004). It has also been demonstrated that physical activity can influence levels of inflammation in a variety of populations (Reuben et al. 2003, Pitsavos et al. 2003, Yates et al. 2008) and thus is likely to have an impact upon this CVD risk factor.

The aim of this overview is three-fold. Firstly, an understanding of the reasoning for the increased CVD risk in the RA population is presented. Secondly, particular regard is paid to the links between inflammation, in particular inflammatory markers, and CVD risk. Thirdly, the role that physical activity plays in the modulation of inflammatory markers in both the general and other clinical populations is described and, what is known on the topic in the RA population is also discussed.

4.2 **REASONS FOR THE INCREASED RISK OF CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS**

The reasons and exact processes leading to the increased cardiovascular mortality rate in this population are not completely understood. It is likely that numerous factors are at play and include: traditional cardiovascular risk factors, the side effects
of some anti-rheumatic and other drug treatment, and non-traditional cardiovascular risk factors (some specific only to the RA population).

Traditional cardiovascular risk factors can be divided into modifiable and non-modifiable risk factors. Modifiable factors include hypertension, diabetes, physical inactivity, dyslipidaemia, stress, smoking, obesity, heavy alcohol intake, insulin resistance and hyperglycemia. Non-modifiable factors include male sex, older age, and family history of cardiovascular events.

According to Peters et al. (2010) traditional cardiovascular risk factors probably occur more frequently among the RA population however the evidence is not convincing either way and adequate studies are lacking. Metsios et al. (2008b) reiterates this finding reporting that “classical modifiable CVD factors are highly prevalent but under-investigated and suboptimally managed” in RA. Investigations into traditional risk factor prevalence in the RA population demonstrate that diastolic blood pressure is significantly higher in individuals with RA compared to controls (McEntegart et al. 2001), RA patients are more likely to be smokers or have smoked (McEntegart et al. 2001, Brady et al. 2009) and are more likely to be physically inactive (Brady et al. 2009) when compared to controls. Conversely, Solomon et al. (2004) suggested that the frequency of most of the traditional risk factors for CVD are similarly distributed in RA patients and controls.

Drugs used in the management of RA have the potential to effect cardiovascular risk and indeed many of the drugs used by individuals with RA have been shown to be associated with increased life expectancy with regard to cardiovascular health because of their beneficial effects on inflammation which results in a lowered cardiovascular risk profile. This has been shown to be the case for many of the disease modifying anti rheumatic drugs (DMARDs) including methotrexate (Westlake et al. 2010), hydroxychloroquine (Young Hee Rho et al. 2009) and tumor necrosis factor (TNF) inhibitors (Jacobsson et al. 2005). Furthermore, HMG-CoA reductase inhibitors (statins) are sometimes prescribed in the RA population for their anti-inflammatory and immunomodulatory properties (Nurmohamed 2009, Tandon et al. 2005). However the primary role of these drugs is in relation to their cholesterol
lowering properties, thereby causing effect on one of the traditional CVD risk factors.

However, this is not the case for all drugs used in the management of this condition and the effect of pharmacotherapy is more complex. Findings of negative cardiovascular effects of some drugs used in the treatment of RA patients have been verified in a recent EULAR (EUropean League Against Rheumatism) evidence based recommendation on cardiovascular risk management for patients with inflammatory arthritis (Peters et al. 2010). Non steroidal anti inflammatory drugs (NSAIDS) have been shown to be associated with hypertension (Ambrose et al. 2009, Johnson et al. 1994) and in particular ibuprofen and diclofenac in high doses are associated with a moderate increase in the risk of vascular events (Kearney et al. 2006). Leflunomide has also been associated with an increased risk of hypertension (Nurmohamed et al. 2002, Rozman et al. 2002). Cyclooxygenase II inhibitors (COXIbs) are associated with an increased risk of thrombo-embolic events (Ambrose et al. 2009) and a moderate increase in the risk of vascular events (Kearney et al. 2006). Furthermore, there is good evidence to support the suggestion that regular treatment with corticosteroids is associated with an increase in the incidence of a major cardiovascular event (Maxwell et al. 1994, Souverein et al. 2004, Wei et al. 2004), and although it has an effect irrespective of the dose, greatest changes are noted with higher intakes. In addition the bisphosphonates are widely prescribed in these patients with multiple risk factors for osteoporosis and bisphosphonates have been demonstrated to have independent effects on many pro-inflammatory cytokines (Marcuzzi et al. 2010). However, because these drugs interface with so many different elements of the genome, it is not possible to fully understand all of their potential effects.

Nonetheless, despite the potentially less favourable distribution of CVD risk factors in patients with RA and the deleterious effects of some drugs used in the management of RA, these two reasons do not fully explain the increased risk of CVD in the population. Much attention has been paid to the potential role of high grade systemic inflammation and its role in further negatively impacting on the cardiovascular risk profile of this population. At present, the key feature explaining
the increased cardiovascular risk in this population appears to centre on inflammation (Peters et al. 2010).

4.3 INFLAMMATION AND INFLAMMATORY MARKERS AND THE LINKS TO CARDIOVASCULAR DISEASE RISK

The inflammatory process is inherently complex and incompletely understood. Inflammatory markers are specific markers which may be raised or decreased in response to inflammation. As RA is an inflammatory arthritis, it is beneficial to monitor these specific markers in order to assess the level of inflammation and in turn disease activity. The inflammatory cascade is best considered a complex perpetually changing milieu of interdependent factors and to simplify its complexity is all too easy. However in order to offer some understanding, we must adopt a construct with which to work.

Propagation of the inflammatory response is initiated when inflammatory markers become mobilised after a disturbance in homeostasis occurs. This is often due to infection, injury, neoplastic growth or immunological disorders. This leads to a local reaction with activation of leukocytes, fibroblasts and endothelial cells which stimulates the release of cytokines, in particular interleukin 6 (IL-6), interleukin 1 (IL-1), TNF and interferons (Heinrich et al. 1990). IL–6 is a pleiotropic cytokine, commonly produced at local tissue sites and released into circulation in almost all situations of homeostatic perturbation (Xing et al. 1998). TNF is also a pleiotropic cytokine involved in systemic inflammation. IL-1 is another cytokine which often acts synergistically with TNF during the pro-inflammatory process.

The release of these cytokines results in a systemic reaction with the hypothalamus, hypophysis, liver, bone marrow and immune system all becoming involved (Heinrich et al. 1990). The liver in particular has a major effect on inflammatory blood markers as it produces acute phase proteins. These acute phase proteins include C-reactive protein (CRP), Serum Amyloid A (SAA) and fibrinogen. CRP is one of the most commonly assessed markers of inflammation in the RA population. It is the prototype acute phase protein and can increase up to 1000 fold after the onset of a stimulus (Ablij and Meinders 2002). SAA is another of the prominent acute phase
proteins in humans. In inflammation, the serum concentrations of SAA may also reach levels that can be up to 1000 fold greater than the non-inflammatory state (Sodin-Semrl et al. 2006, Hatanaka et al. 2004). Fibrinogen is a protein, formed in the liver, that plays a key role in blood clotting (Weisel 2005). Though fibrinogen represents a small fraction of plasma proteins, when converted to fibrin by the action of thrombin in the presence of ionised calcium can cause a gelation, which serves to block the flow of blood (Weisel 2005).

These acute phase proteins in conjunction with influence from the bone marrow and immune system’s systemic reaction involvement will impact upon the blood resulting in leukocytosis, complement activation and increase of erythrocyte sedimentation rate (ESR). Leukocytosis is strongly associated with future CVD (Núñez et al. 2006) and the participation of leukocytes in the pathogenesis of ischemic damage have been clearly demonstrated (Núñez et al. 2006). The major influence on the rate of sedimentation of erythrocytes is the degree to which they aggregate with each other (Jurado 2001), caused by electrostatic forces. These cells normally have a net negative charge and repel each other. However, many of the acute phase proteins are positively charged which allows for neutralisation of the surface charge of erythrocyte, thereby reducing the repulsive forces and promoting aggregation (1986). The end point of the inflammatory cascade as best we understand is the production of effector proteinases of matrix metalloelastase which initiate numerous actions from bone turnover to neovascularisation. It is at this level we see many of the structural end points inflammation causes including atherosclerotic plaque formation and instability.

The effect of rheumatoid cachexia on CVD must also be taken into consideration. In rheumatoid cachexia, patients suffer an accelerated loss of lean body mass (LBM), with a maintenance or increase in fat mass to ensure that body weight and body mass index (BMI) can remain relatively stable (Roubenoff 2009). Therefore, these patients have increased levels of fat and adipose tissue when compared to others of the same BMI. The extent to which adipose tissue directly produces or indirectly induces the production of cytokines is still under investigation, but it is widely accepted that pro-inflammatory cytokine levels (such as IL-1, IL-6 and TNF-α) increase and anti-
inflammatory cytokine levels (such as adiponectin and IL-10) decrease with increasing adiposity (Juge-Aubry et al. 2005, Stavropoulos-Kalinoglou et al. 2007).

Recent work has helped define a pathophysiological link between coronary atherosclerosis and inflammation (Berrahmoune et al. 2005, Ross 1999, Libby et al. 2002). It has been shown that fatty streaks, the earliest atherosclerotic lesions, contain macrophages and t-lymphocytes and are rich in inflammatory cytokines such as TNF-α, IL-1 and IL-2. In fact, inflammatory mechanisms play a fundamental role in mediating all phases of atherosclerosis from initial recruitment of circulating leucocytes to the arterial wall to eventual rupture of an unstable plaque. Furthermore, the suggestion that systemic inflammation can enhance atherogenesis has been substantiated by the observation that various anti-inflammatory interventions can protect against it. For instance, blockade of cytokines, in particular TNF has been shown to result in effective suppression of inflammation and ultimately a decreased cardiovascular risk in RA (Jacobsson et al. 2005, Nurmohamed et al. 2002).

Because of the central role that inflammation plays in all phases of atherosclerosis, attention has begun to focus on whether circulating levels of markers of inflammation may help identify those at high risk of future cardiovascular events.

Inflammatory markers have been shown to predict coronary heart disease (CHD) in long term prospective studies in healthy subjects. It has been demonstrated by Cesari et al. (2003) that participants with incidents of CHD, stroke and congestive heart failure (CHF) at follow up had higher levels of IL-6 at baseline. TNF-α levels were higher at baseline in those with CHD and CHF events at follow up, while high baseline CRP levels were demonstrated in those who had CHF events at follow up. Similarly, Pai et al. (2004) found in women in whom CHD developed during follow up had significantly higher baseline levels of TNF soluble receptor types 1 and 2 than those women who did not develop the disease (controls). In the case of both men and women, CHD patients at follow up had significantly higher baseline levels of CRP and IL-6 than controls.

With specific regard to the RA population, the results remain similar, although not in prospectively conducted studies. Rho et al. (2009) concluded that TNF-α and IL-6 are significantly associated with severity of subclinical atherosclerosis as measured
by coronary artery calcification. Foster et al. (2009) found correlations between IL-6 and vascular endothelial growth factor, which is used as a plasma marker of angiogenesis. Using carotid artery intra-media thickness (IMT) as an assessment of atherosclerosis, del Rincon et al. (2001) found a significant linear trend for increased carotid artery IMT associated with increased levels of ESR and CRP. This was found independent of age, sex and other cardiovascular risk factors including blood pressure, BMI, diabetes mellitus and hypercholesterolemia.

The results of the research conducted to date show that inflammatory marker levels may indeed indentify those at higher cardiovascular risk in both the RA and other populations. Given that individuals with RA have a disease characterised by high grade inflammation of a chronic nature, they may resultantly be particularly prone to atherosclerosis and long term risk of CVD. Systemic inflammation confers a statistically significant additional risk for cardiovascular death among patients with RA, even after controlling for traditional risk factors and co morbidities (Maradit-Kremers et al. 2005)

Given the importance of inflammation in the development of CVD, therapies aimed at reducing the systemic inflammation may also have a positive impact on CVD risk, particularly in RA. Traditionally, inflammation has been managed by pharmacotherapy in this population; however there is evidence to show that inflammatory marker levels can be reduced through more holistic measures such as physical activity.

4.4 Effect of Physical Activity on Inflammatory Markers in Other Populations

Recent research has shown that physical activity has the ability to influence inflammatory marker levels and thus potentially lower CVD risk. Much of the research conducted to date to assess the effect of physical activity on inflammatory markers has focused attention primarily or uniquely on the impact physical activity has on CRP. A systematic review carried out by Kasapis and Thompson (2005) found that cross sectional studies in the area demonstrate an inverse relationship between regular physical activity levels and CRP concentration.
In a wider range of inflammatory markers, the general consensus from the mainly cross-sectional literature conducted to date is that high physical activity levels are inversely related with inflammatory marker counts in a range of populations (Table 4.1).

While no causation can be inferred from cross-sectional studies the overriding result of these studies, namely that the most active individuals have the lowest levels of inflammatory markers, infers that physical activity has anti-inflammatory effects. This anti-inflammatory effect may explain in part the association between CVD risk reduction and physical activity.

Converse to the predominant finding of high physical activity levels being associated with lower inflammatory marker levels, Verdaet et al. (2004), found that leisure time physical activity was not an independent predictor of CRP, SAA or fibrinogen levels. However, this finding is in the minority. With regard to the Verdaet et al. (2004) study, Kasapis and Thompson (2005) propose that the lack of an inverse relationship may be as a result of the high proportion of sedentary subjects in this study (almost 63% of subjects reported no or low leisure time physical activity).

A wide range of inflammatory markers have been assessed in the studies outlined in Table 4.1. Many of the inflammatory markers assessed have shown inverse relationships with physical activity, with some others not demonstrating significant differences. However, the authors of this overview acknowledge that the studies included here are not an exhaustive list of all those published on this topic and a systematic review may be warranted in order to pool together the data from the varying inflammatory markers.

The mechanism of how physical activity influences inflammation remains unclear to date. However, Bruunsgaard (2005) and Woods et al. (2009) make some suggestions to explain some of the potential mechanisms. These include: (a) its effect in reducing inflammatory marker secreting adipose tissue and (b) the increase of IL-6 levels after acute activity which works to modulate the pro-inflammatory effects of TNF in the longer term. These and the other suggestions put forward have not been proven however, and further investigation to confirm or negate these hypotheses is deemed necessary (Bruunsgaard 2005, Woods et al. 2009).
**TABLE 4.1 METHODOLOGY AND OVERALL RESULTS OF STUDIES**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Number</th>
<th>Age Range / Mean age ± SD</th>
<th>Physical Activity Measurement Tool</th>
<th>Inflammatory Markers Assessed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefkken et al. (2001)</td>
<td>Healthy elderly population</td>
<td>5,888</td>
<td>≥ 65 years</td>
<td>Instrument adapted from the Health Interview Study</td>
<td>CRP, Fibrinogen, Factor VIII, WBC, Albumin</td>
<td>Compared with persons in the lowest quartile, those in the highest quartile of physical activity had 19%, 6%, 4%, and 3% lower concentrations of CRP, WBC, Fibrinogen and Factor VIII activity respectively after adjustment. These were statistically significant findings.</td>
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<td>Reuben et al. (2003)</td>
<td>High-Functioning Older Persons</td>
<td>870</td>
<td>70 – 79 years</td>
<td>Self-reported physical activity using questions modified from the Yale Physical Activity Survey MacArthur Battery to assess housework and yard work activities</td>
<td>CRP, IL-6</td>
<td>Persons who had high total physical activity (top 50%) had significantly lower CRP and IL-6 levels than those who had low total physical activity (bottom 50%). The CRP levels showed statistical significance.</td>
</tr>
<tr>
<td>Colbert et al. (2004)</td>
<td>Well-functioning Older Adults</td>
<td>2,964</td>
<td>70 – 79 years</td>
<td>Interviewer-administered questionnaire on whether they had performed</td>
<td>CRP, IL-6, TNF-α</td>
<td>Statistically significantly higher levels of activity were associated with lower levels of CRP, IL-6 and TNF-α</td>
</tr>
<tr>
<td>Study</td>
<td>Group Description</td>
<td>Sample Size</td>
<td>Age Range</td>
<td>Method of Physical Activity Assessment</td>
<td>Assessed Biomarkers</td>
<td>Comparison</td>
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<tr>
<td>Pitsavos et al. (2003)</td>
<td>Healthy Subjects</td>
<td>1,856</td>
<td>&gt;18 years</td>
<td>A self-reported questionnaire was applied by trained interviewer based on a special questionnaire for the assessment of leisure-time physical activity</td>
<td>High Sensitivity CRP, WBC, Amyloid A, Fibrinogen</td>
<td>Compared with those who reported a sedentary lifestyle, those who were defined as highly physical active had 33% lower concentration of high sensitivity CRP, 10% lower WBC counts, 17% lower concentration of amyloid A and a 3% lower fibrinogen level. High sensitivity CRP and WBC count were statistically significant</td>
</tr>
<tr>
<td>Panagiotakos et al. (2005)</td>
<td>Healthy Subjects</td>
<td>3,042</td>
<td>&gt;18 years</td>
<td>Assessed by considering frequency, duration and intensity of sports-related physical activity during a usual week</td>
<td>CRP, SAA, IL-6, fibrinogen, WBC, TNF- α</td>
<td>Highly physical active individuals had 29%, 19%, 22%, 20%, 32%, and 11% lower levels of CRP, WBC, SAA, TNF- α, IL-6 and fibrinogen respectively when compared to sedentary ones. These findings were statistically significant.</td>
</tr>
<tr>
<td>Borodulin et al. (2006)</td>
<td>Healthy Subjects</td>
<td>3,803</td>
<td>25 – 74 years</td>
<td>Leisure time physical activity was assessed by a self-administered validated questionnaire</td>
<td>High sensitivity CRP</td>
<td>An inverse age-adjusted statistically significant association of conditioning and non-conditioning physical activity</td>
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</table>


<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Age Range</th>
<th>Activity Measurement</th>
<th>Inflammatory Markers</th>
<th>Findings</th>
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</table>
| Autentieth et al. (2009)                                             | General population                  | 796         | 35 – 74 years | 12-month recall incorporating conditioning, commuting and non-conditioning physical activity | Fibrinogen, CRP, IL-6 | Commuting physical activity was statistically significantly associated with CRP in women only.  
Fibrinogen, CRP and IL-6 showed statistically significant inverse relationships with higher levels of physical activity |
<p>| McDermott et al. (2004)                                             | Patients with peripheral arterial disease | 188         | ≥ 55 years | 7 day measurement using Caltrac vertical accelerometer                              | CRP, fibrinogen, SAA | In age-adjusted analyses, lower physical activity quintiles were associated linearly and significantly with higher levels of CRP, fibrinogen and SAA |
| Yates et al. (2008)                                                 | Individuals screened for type 2 diabetes | 400         | 61.8 ± 9.1 | International Physical Activity Questionnaire (IPAQ)                                 | TNF-α, IL-6 and high sensitivity CRP | After adjustment, those who reported walking for at least 30 minutes on at least 5 days/week had statistically significantly lower levels of CRP, IL-6 and TNF-α than those who did not. |
| Verdaet et al. (2004)                                               | Healthy subjects                    | 892         | 35 – 59 49.4 ± 5.4 | Self-reported leisure time physical activity, including SAA, ultra sensitive CRP, fibrinogen | SAA, ultra sensitive CRP, fibrinogen | After adjustment, no significant relationship was found between leisure |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Group Description</th>
<th>Sample Size</th>
<th>Activity Measures</th>
<th>Metrics</th>
<th>Results</th>
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<tr>
<td>Dixon et al. (2009)</td>
<td>Healthy males</td>
<td>25</td>
<td>Actiheart combined heart rate and accelerometer measurement for 7 whole consecutive days</td>
<td>CRP, IL-6</td>
<td>Active men had statistically significantly lower fasting levels of IL-6 and CRP than sedentary men</td>
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All recreational activities and house- and yard-work.
4.5 Effect of Physical Activity on Inflammatory Markers in Rheumatoid Arthritis

To date, little research has been conducted in this area in the RA population, despite the higher prevalence of inflammation and resultant inflammatory markers indicative of this group. The authors of this overview were only able to source two papers (Metsios et al. 2009, Elkan et al. 2011) on this topic. Using the long version of the International Physical Activity Questionnaire (IPAQ), Metsios et al. (2009), allocated 65 RA patients into three groups: active, moderately active and inactive and assessed two inflammatory markers CRP and fibrinogen. Statistically significant differences were detected among groups for the inflammatory marker fibrinogen dependent on activity levels. CRP was not found to demonstrate significant differences. Furthermore, it is important to note that differences were also noted in traditional CVD risk factors and also coagulation- and metabolism-related non traditional CVD risk factors in this study. More recently, Elkan et al. (2011) aimed to assess if total physical activity was associated with a range of cardiovascular risk factors, including inflammatory markers. The authors of this study utilised the short form self-administered IPAQ to assess average total physical activity during the previous year, and then divided subjects into quartiles based on their metabolic equivalent (MET) hours. No statistically significant differences were found in the levels of the assessed inflammatory marker, ESR between those in the MET-hours 1st quartile compared to those in the MET-hours 4th quartile, although a trend was evident.

Although, fibrinogen was the only inflammatory marker which demonstrated an association with physical activity levels in the two previously mentioned studies (Metsios et al. 2009, Elkan et al. 2011), this is not to definitely state that there is no association between physical activity and other inflammatory markers. A larger range of inflammatory markers should be assessed as has been investigated in other populations. This may allow for the demonstration of which, if any, inflammatory markers have associations with physical activity levels. It may be necessary to assess high sensitivity CRP rather than the standard test as it is more specific particularly at lower concentrations of the protein. This has been carried out in the previously discussed studies by Borodulin et al. (2006), Yates et al. (2008) and Pitsavos et al.
(2003), with positive findings. Furthermore, the use of an objective physical activity measurement tool which has been validated in the RA population may be necessary, as bias may occur with the use of subjective tools and tools which may not be suitable for use in the specific population. Furthermore, neither Metsios et al. (2009) or Elkan et al. (2011) reported on their power calculations. It may be the case that with the inclusion of a larger sample some of the inflammatory markers which did not demonstrate significant findings may indeed show significance.

However, it may in fact be that the results of these preliminary studies do accurately reflect the case in the RA population. The higher degree of inflammation evident in the RA population as well as the autoimmune nature of this inflammation may play a role and could, at least in part, explain the difference in the effect physical activity plays on inflammation in this population compared to the healthy population. Again, larger powered studies, with a wider range of inflammatory markers will help to prove or negate this hypothesis.

4.6 Conclusion

The exact causes for the increased CVD risk in the RA population have not yet been determined. The impact of traditional CVD risk factors and pharmacotherapy in RA may prove causative. However, increasingly it has been recognised that inflammation plays an important role in atherosclerosis and inflammatory markers have been linked to CVD. Because inflammation is such an intrinsic part of RA, methods of reducing inflammation may have an effect on reducing CVD risk. In the general population, physical activity has been shown to alter inflammatory marker levels, thus inferring its role in modulating CVD risk. However, little research has been conducted on the effect in RA, and further high quality research is necessitated.
CHAPTER 5 A STUDY TO DETERMINE THE CRITERION VALIDITY OF THE SENSEWEAR ARMBAND AS A MEASURE OF PHYSICAL ACTIVITY IN PEOPLE WITH RHEUMATOID ARTHRITIS

(Tierney M. Fraser A. Purtill H. and Kennedy N. “A study to determine the criterion validity of the SenseWear Armband as a measure of physical activity in people with rheumatoid arthritis”. Arthritis Care and Research (In press DOI: 10.1002/acr.21914))
5.1 INTRODUCTION

Regular physical activity is associated with improvements in health, in particular improvements in cardiovascular health, in many populations. Recent studies assessing physical activity in the general adult population have shown a decreased incidence in CVD in more physically active subjects in a graded manner (Aadahl et al. 2009, McGuire et al. 2009, Valle et al. 2004). Physical activity has been shown to both prevent and help treat many established atherosclerotic risk factors (Thompson et al. 2003). While a few studies (Roubenoff et al. 2002, Raftery et al. 2009, Hagfors et al. 2005, Piva et al. 2010) have objectively measured levels of physical activity in people with RA, it has not been definitively determined if physical activity is reduced in this population (Tierney et al. 2012b). In advance of objective measurement to determine this, it is imperative that the physical activity measurement tool to be used is validated in the population in which it will be used (Welk 2005, Warms 2006). Validation should be undertaken to establish criterion validity against a gold standard measure of physical activity measurement. As the construct of interest is physical activity in the field setting, validity during a range of daily tasks needs to be undertaken, rather than a treadmill walking protocol, which does not reflect the activities typically occurring in the field setting.

Physical activity is ‘any bodily movement produced by skeletal muscles that results in energy expenditure’ (Caspersen et al. 1985) and is typically measured by recording movement (generally in the form of step counts) or energy expenditure (Thomas et al. 2005).

As both the amount of movement (step count) and intensity (energy expenditure) of physical activity is recorded by SWA, it is an obvious choice to measure those parameters in the RA population. The validity of the SWA to estimate step counts and energy expenditure has not been established in this population, despite its recent use to estimate levels of physical activity by a number of authors (Piva et al. 2010, Almeida et al. 2011).

Thus, the purpose of this study is to evaluate the criterion validity of SWA to estimate 1) step count when compared to the criterion measure, manual count of steps during video observation, and 2) to estimate energy expenditure compared to
the criterion measure, indirect calorimetry, during activities of daily living (ADL’s) in people with RA.

5.2 METHODOLOGY
5.2.1 SUBJECTS
Fourteen participants (eight male, six female) with a diagnosis of RA according to American College of Rheumatology (ACR) criteria (Arnett et al. 1988) were recruited from rheumatology clinics at the Mid Western Regional Hospitals, Limerick, Ireland to participate in this study. All subjects were over 18 years of age, were on a stable drug regime in the previous three months, were not pregnant and were ambulatory with a maximum of one unilateral aid. The procedures were reviewed and approved by the Mid Western Regional Hospital Ethics Review Board, Limerick prior to the beginning of the study.

Upon arrival at the testing centre, each subject provided written informed consent before participating in the study. Date of birth and self reported disease duration were recorded and the height and weight of the subjects were measured using a Seca height measure (Birmingham, UK) and a Salter mechanical scale (Kent, UK) respectively, with subjects wearing a t-shirt and shorts and with shoes removed. Body mass index was calculated according to the formula:

\[
\text{Body mass (kg)} \div \text{height squared (m}^2)\).
\]

5.2.2 SENSEWEAR ARMBAND (SWA)
As previously outlined in Chapter 2.

5.2.3 VIDEO OBSERVATION
The entire testing protocol was recorded using the JVC Everio camcorder and one of the authors (MT) subsequently manually counted the steps from this video. A step was defined as “foot contact with the ground in the sagittal or frontal plane with movement in the same direction”. Manual step count from video observation is considered to be the gold standard for step count in lab-based controlled environments (Schneider et al. 2004), and thus was used as the criterion standard for step count in this study.
5.2.4 INDIRECT CALORIMETRY
Subjects were also fitted with the Oxycon mobile indirect calorimetry system (CareFusion, San Diego, CA, USA) with facemask. This acted as the criterion measure for energy expenditure. The Oxycon mobile is a light; battery operated wireless portable ergospirometry system that is mounted to the subject’s body via a vest. It allows determination of a subject’s metabolic response. Data was recorded on a breath-by-breath basis and collected through a facemask which sent it to a host computer via wireless transmission (Arvidsson et al. 2009).

All measurement tools were comparable from a time perspective due to computer synchronisation.

5.3 PROTOCOL
Participants performed a standardised routine consisting of various lifestyle and housework activities with tasks of varying activity intensities included. Testing was undertaken in a laboratory setting. Before the commencement of the protocol, individuals were asked to rest quietly in a lying position for 30 minutes to ensure a resting state was achieved. The activities included were dressing, walking at a self selected speed, reading, washing and drying dishes, stair climbing (upstairs and downstairs), writing, cleaning and folding laundry. Activities were performed in the order outlined and each activity lasted for a duration of ten minutes with the exception of the stair climbing task which was for five minutes. This order was chosen as it allowed activities of higher intensity to be followed by activities of lower intensity.

Activities in the protocol were chosen based on those included in the Evaluation of Daily Activity Questionnaire (EDAQ) which was used by Nordenskiold et al. (1998) in individuals with RA. It also encompassed activities exhibiting a range of varying MET intensities as defined by Ainsworth et al. (2000) and was also based upon the protocols utilised by Crouter et al. (2008) in their validation studies on the Actiheart physical activity monitor.

The total activity category encompassed the entire protocol. The activity protocol was also broken down into Class A (3 - 5 METS), Class B (2 - 3 METS) and Class C
(1 - 2 METS) intensity activities based on the updated Compendium of Physical activities (Ainsworth et al. 2000). Based on this, Class A was composed of walking, stair climbing and cleaning tasks, Class B was composed of dressing, washing and drying dishes and folding laundry while Class C encompassed reading and writing tasks.

5.4 DATA PROCESSING

5.4.1 SWA
Before each subject began the ADL protocol, the subject’s details (age, height, weight, gender, handedness and smoking status) were entered into the SWA software programme (InnerView Research Software v6.1, Bodymedia). After completion of the protocol, the SWA data was uploaded to the software programme which uses proprietary algorithms developed by the manufacturers to estimate both step count and energy expenditure values from the accelerometry, physiological sensors and demographic data. Both step count and energy expenditure values were computed to one minute intervals which were converted to values for each activity. Energy expenditure values were reported in kcals which were converted to the SI measurement of kJ using the formula:

\[ 1 \text{ kcal} = 4.184 \text{ kJ} \]

5.4.2 OXYCON MOBILE
The system was switched on 30 minutes before the beginning of the protocol as specified by manufacturers’ guidelines. Ambient condition data was inputted and the sensor unit and CO\(_2\)/O\(_2\) calibration was conducted in accordance with the guidelines supplied by the manufacturers. The data was processed by the PC-software (JLAB, CareFusion, San Diego, CA, USA) which allowed for display and storage of the recorded data. Energy expenditure was calculated from the gas exchange data through the use of the Weir equation. Values were provided in kcals/day at 30 second intervals which was converted to energy expenditure (kcals) for each activity. Again kcals were converted to kJ using the previously mentioned formula.
5.5 Data Analysis

SWA was compared to manual step count to assess step count agreement and to Oxycon mobile indirect calorimetry output to assess energy expenditure agreement. This was done in terms of the total protocol and also when the protocol was divided into Class A, B and C categories.

Data were assessed for normality using Shapiro-Wilk statistic and examination of histograms and quantile-quantile plots. All data were found to be reasonably normally distributed.

The validity of SWA as a measure of physical activity, when compared to manual step count and Oxycon mobile, was assessed using the 95% limits of agreement (LOA) in Bland and Altman plots for the total protocol and at the Class A, B and C categories. In the Bland and Altman analyses, 95% confidence intervals were computed for mean pairwise differences and used to assess whether SWA over or under estimated energy expenditure.

A two-way mixed, single measure, interclass correlation [ICC (3,1)] was used to assess the extent of agreement between SWA and the criterion measures for both step count and energy expenditure. The benchmarks for ICC set forth by Landis and Koch (1977) we used, whereby 0.00 – 0.20, 0.21 – 0.40, 0.41 – 0.60, 0.61 – 0.80 and 0.81 – 1.00 indicate poor, fair, moderate, substantial and almost perfect agreement respectively.

Pearson’s correlation coefficient statistic was used to analyse the strength and direction of the relationship between SWA’s assessment of both step counts and energy expenditure and the respective gold standard measures. The benchmarks for correlations set forth by Cohen (1988) were used whereby r = 0.10 – 0.29 was considered small, r = 0.30 – 0.49 was considered medium and r = 0.50 – 1.0 was considered strong.

Statistical analysis was performed using SPSS, version 19.0 for Microsoft Windows.
5.6 RESULTS

Fourteen participants were recruited and performed all the activities in the protocol. Descriptive data for the study participants are presented in Table 5.1.

### TABLE 5.1 DESCRIPTIVE CHARACTERISTICS OF STUDY PARTICIPANTS

<table>
<thead>
<tr>
<th></th>
<th>Total Group (N=14) Mean (SD)</th>
<th>Males (N=8) Mean (SD)</th>
<th>Females (N=6) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.43 (6.80)</td>
<td>65.18 (8.56)</td>
<td>63.42 (3.94)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.3 (12.0)</td>
<td>79.1 (8.2)</td>
<td>74.8 (16.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.2 (6.6)</td>
<td>171.9 (6.9)</td>
<td>165.6 (4.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9 (3.4)</td>
<td>26.8 (1.8)</td>
<td>27.2 (5.0)</td>
</tr>
<tr>
<td>Length since diagnosis (years)</td>
<td>12.4 (13.2)</td>
<td>10.8 (11.6)</td>
<td>14.6 (16.0)</td>
</tr>
</tbody>
</table>

5.6.1 STEP COUNT

SWA underestimated step counts during the protocol as a whole and during each of the three intensity categories (Table 5.2, Fig. 5.1). With regard to the total activity category, the ICC for the agreement between SWA and manual step count was 0.304 (p=0.038). Bland and Altman analysis show a mean difference of 554.64 steps (95% CI: 279.92, 829.37), a standard error of the difference of 140.16 and a standard deviation of the difference of 524.45 (Table 5.2).

When assessing different classes of activities, SWA also demonstrated similarly low ICC agreement between SWA and manual step count for both Class A and Class B intensity activities as it did for the total activity category, with ICC values of 0.334 (p=0.022) and 0.351 (p=0.069) respectively. Bland and Altman analysis also showed results on a similar level to that of the total activity category (Table 5.2). SWA’s ability to determine step counts at lower intensity activities (Class C) was extremely poor with an ICC agreement between SWA and manual step count of -0.130 (p=0.75).
TABLE 5.2 BLAND AND ALTMAN TABLE FOR STEP COUNT (SWA)

<table>
<thead>
<tr>
<th>Intensity Category</th>
<th>Bland and Altman (SWA prediction of Step Count)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d (steps)</td>
</tr>
<tr>
<td>Total</td>
<td>554.64</td>
</tr>
<tr>
<td>Class A</td>
<td>460.14</td>
</tr>
<tr>
<td>Class B</td>
<td>78.36</td>
</tr>
<tr>
<td>Class C</td>
<td>17.86</td>
</tr>
</tbody>
</table>

Key: d (mean differences), SE (standard error), CI (confidence interval), SD_{diff} (standard deviation of the differences), LOA (limits of agreement)

FIGURE 5.1 BLAND AND ALTMAN PLOT FOR TOTAL STEP COUNT (SWA)
5.6.2 ENERGY EXPENDITURE

A summary of the Bland and Altman analyses comparing SWA to Oxycon mobile for the energy intensity categories and for total energy expenditure is presented in Table 5.3.

TABLE 5.3 BLAND AND ALTMAN TABLE FOR ENERGY EXPENDITURE (SWA)

<table>
<thead>
<tr>
<th>Intensity Category</th>
<th>Bland and Altman (SWA prediction of Energy Expenditure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d (kJ)</td>
</tr>
<tr>
<td>Total</td>
<td>-182.48</td>
</tr>
<tr>
<td>Class A</td>
<td>-71.83</td>
</tr>
<tr>
<td>Class B</td>
<td>-147.30</td>
</tr>
<tr>
<td>Class C</td>
<td>36.61</td>
</tr>
</tbody>
</table>

Key: d (mean differences), SE (standard error), CI (confidence interval), SD_{diff} (standard deviation of the differences), LOA (limits of agreement)

For total energy expenditure, SWA shows substantial agreement (ICC = 0.717, p<0.001) for agreement with Oxycon mobile and a high correlation value of 0.852, showing a strong positive linear relationship between the measures. Bland and Altman analyses demonstrate that for the total protocol, SWA overestimates energy expenditure (Table 5.3). The Bland and Altman plot, Fig 5.2 shows a mean difference of -182.48kJ. The 95% confidence interval for this mean difference is -273.11 to -91.84 (Table 5.3), representing an overestimation of energy expenditure by SWA when compared Oxycon mobile for the total protocol.
The ICC values for the agreement between SWA and Oxycon for Class A, B and C activities are 0.684 (p=0.001), 0.471 (p<0.001), 0.505 (p=0.001) respectively and correlations highlighting the strength of the relationship were found to be 0.767, 0.809 and 0.776 respectively.

However, similar to the findings for the total activity category, Bland and Altman analyses, shows that SWA overestimates energy expenditure for categories A and B, having mean differences and associated 95% confidence intervals of -71.83 (95% CI: -128.74, -14.92) and -147.30 (95% CI: -191.23, -103.37), respectively. In the case of the low intensity category C, SWA underestimates energy expenditure with a mean difference of 36.61 (95% CI: 20.23, 52.99).

5.7 DISCUSSION
This is the first study to examine the criterion validity of SWA to estimate step count and energy expenditure in people with RA. The validity was assessed by comparing the outputs (step counts and energy expenditure) of the SWA with simultaneous measurement of step count and energy expenditure by the criterion standards of manual step count and indirect calorimetry. This study has found that SWA is not
valid to estimate step counts after analysis with by ICC, Bland and Altman and correlational methods.

Conversely, this study has found that SWA demonstrates moderate to substantial agreement and a strong relationship with the Oxycon mobile when assessing energy expenditure during a range of everyday activities in individuals with RA. However, Bland and Altman analyses shows that SWA overestimates energy expenditure for the total activity category, classes A and B and underestimates energy expenditure for class C category.

Validation studies of tools to measure physical activity are limited within clinical populations and this study is unique within the RA population. The results of this study must be interpreted in the context of the other measurement properties of the tool. There is a lack of research investigating the reliability of SWA to measure steps however of late; there have been studies conducted which indicate that SWA is a reliable tool to estimate energy expenditure in healthy adults (Brazeau et al. 2011), in obese subjects (Papazoglou et al. 2006, Malavolti et al. 2012) and in COPD subjects (Hill et al. 2010). Thus, although the reliability has not been established in the RA population (which we would recommend be carried out), the good reliability of SWA to estimate energy expenditure established in other population groups and the proven validity described by the present study ensures that SWA, as a measure of energy expenditure in this population, is among the most suitable and should be recommended for use in both clinical practice and the research setting.

5.7.1 STEP COUNT
The computed ICC values for the agreement between SWA and manual step count for the activity categories represent poor agreement and indicate that SWA is not a valid tool for predicting step counts in this population. The Bland and Altman analyses also show poor agreement between SWA and manual step counts. The mean difference of 554.64 steps for the total activity category in a 75 minute protocol must be considered in the larger context of a 24 hour day or indeed seven day week.

Although Dwyer et al. (2009), in a cystic fibrosis population, found SWA to be a “reasonably accurate estimate” (p1516) of step count, this was in 20 minute treadmill walking protocol which is more likely to have strong foot contact with the ground
and definite arm swing allowing the accelerometer threshold for a step to be achieved. During the ADL protocol utilised in this study, steps were recorded during activities such as washing and drying dishes and folding laundry which involved the participants taking steps, but ones which may not have the same foot contact force and definite arm swing as treadmill walking, thus not reaching the threshold necessary to produce a SWA step.

5.7.2 Energy Expenditure
The main finding from the energy expenditure aspect of this study is that the SWA shows moderate to substantial agreement and a strong relationship with Oxycon mobile when assessing ADLs in the RA population, using ICC and correlational analyses. However, from Bland and Altman analyses, SWA is shown to generally overestimate energy expenditure.

It is difficult to compare the results of this study to other studies as no other study has validated an accelerometer based physical activity monitor for use in the RA population. However, when assessing the ability of SWA to estimate energy expenditure in other populations, the findings are variable. SWA tends to underestimate energy expenditure in many of the studies, particularly those validated in free living situations (Berntsen et al. 2010, Johannsen et al. 2010, Jakicic et al. 2004, St-Onge et al. 2007); however there are reports of overestimation particularly in specific populations (Heiermann et al. 2011, Dorminy et al. 2008, Papazoglou et al. 2006) and in studies of treadmill protocols (Fruin and Rankin 2004, King et al. 2004).

The reasons for the overestimation in this specific population are not immediately obvious. A number of factors may be at play including physiological factors. The addition of a physiological variable should provide a better estimation of energy expenditure than accelerometry alone (Crouter et al. 2008). SWA is different to other more traditional physical activity monitors which rely solely on accelerometers to determine energy expenditure. As previously outlined, the SWA not only includes a biaxial accelerometer for motion detection, but additional sensors to monitor heat production, skin temperature and sweat production.
RA is both an inflammatory disorder and one which is characterised by metabolic abnormalities. Rheumatoid cachexia is a concurrent metabolic disorder, affecting almost all of the RA population to some extent (Roubenoff 2008, Walsmith and Roubenoff 2002) which causes hypermetabolism mainly due to excessive TNF-α production (Roubenoff 2008, Metsios et al. 2007). Hypermetabolism is defined as an increase in heat production relative to the observed thermogenesis of a reference population (Heymsfield et al. 1990). When the body’s temperature begins to rise above the normal range, heat-dissipating behaviours such as sweating and vasodilation are initiated (Robertson et al. 2011, Charkoudian 2010). Vasodilation, which is already heightened in the inflammatory state (Metz et al. 2007, Huang and Vita 2006), allows for increased blood flow to all the organs including the skin. Yosipovitch et al (2004) showed that skin blood flow correlates strongly with forearm skin temperature, with increased blood flow resulting in higher skin temperature.

Thus, the heat flux, skin response (sweat) and skin temperature sensors on the SWA would receive increased input due to the heightened heat-dissipation techniques employed by the RA population related to the metabolic abnormalities exhibited by this population. This increased input may be utilised by SWA as input related to increased heat-dissipation due to increased activity rather than the metabolic abnormality in this population. This may, in part, account for the reason why SWA was found to overestimate activity in the RA population.

Furthermore, the largest overestimation found in the present study was found during Class B intensity activities. The activities which made up this category (dressing, washing and drying dishes and folding laundry) are activities which utilise a large degree of upper limb movement. Jakicic et al (2004) found overestimation by SWA of 21.7% in an arm ergometry task, despite finding underestimation in the other activities included in the exercise protocol validated. This may signify that SWA may not be accurately representing energy expenditure accrued during upper limb activities. The positioning of the armband on the upper arm may be contributory to this inaccuracy.
5.8 LIMITATIONS

There are some limitations associated with this study which need to be considered.

Basal metabolic rate of each participant was not recorded and therefore a calibration study of the SWA was not performed. However, the aim of this study was not to make the tool valid for use in this population (calibration study), but rather to assess if it was valid in its current form for use in the population (validation study).

Participants did not complete activities at intensities higher than 5 METS according to values outlined in the Compendium of Physical Activities (Ainsworth et al. 2000). Although we have stated SWA is suitable for use in assessing energy expenditure during ADLs, we are unsure of accuracy at intensities higher than 5 METS and therefore unsure if there is a ceiling effect to SWA’s ability to estimate energy expenditure in this population accurately.

Similar to many other validation studies, it was not feasible for the Oxycon mobile or video analysis to be used in the truly free living situation. Thus this study is the validation of a simulated protocol of typical ADLs, not true free living. However, activities in the protocol were chosen based on those included in the Evaluation of Daily Activity Questionnaire (EDAQ) which was used by Nordenskiold et al. (1998) in individuals with RA. It also encompassed activities exhibiting a range of varying MET intensities as defined by Ainsworth et al. (2000) and was also based upon the protocol utilised by Crouter et al. (2008) in their validation study on the Actiheart physical activity monitor.

The study population were a relatively able population, who used at most one stick. Therefore, it may not be possible to extrapolate the findings to a more disabled population with accuracy.

The relatively small sample size (n=14) may also be a limitation in the present study, with regard to whether the sample is representative of the greater RA population.
5.9 Implications

This study has shown that SWA shows substantial agreement and a strong relationship with the criterion measure, Oxycon mobile indirect calorimetry during ADLs in the RA population. However it does have difficulty accurately estimating the exact energy expenditure values. We believe that this tool can be utilised in the RA population to estimate energy expenditure but regard should be paid to its tendency to overestimate this variable. We would not recommend that SWA should be used to estimate step counts in the RA population.

The proprietary algorithms developed by the manufacturers for use with SWA may need modification for use in the RA population during ADLs, perhaps due to the metabolic abnormalities which are evident in this population. This is in line with the findings of Metsios et al. (2008a) who outlined that development of algorithms specific to the RA population may be necessitated in order for tools to accurately represent energy expended in this population considering the differences of this population to the general population with regard to metabolism. Jakicic et al. (2004) observed that when exercise specific algorithms were developed by the manufacturers, the estimate of energy expenditure produced by the SWA in their healthy population improved. Thus, further work may be necessitated to develop population specific algorithms to calibrate SWA to more accurately represent the energy expenditure of this population.

In conclusion, on account of agreement and correlation analyses, SWA can be considered a valid tool to estimate energy expenditure in the RA population during ADLs; however regard should be paid to its tendency to overestimate. Its ability to estimate step counts could be significantly improved upon and further development of the proprietary algorithms may improve the accuracy of both the step count and energy expenditure outputs and is encouraged.

In summary, SWA is a suitable tool to measure physical activity in the form of energy expenditure in the RA population.
Note: The criterion validity of a further physical activity measurement tool was also determined for this population ¹

¹ A further physical activity measurement tool, the SHIMMER (Sensing Health with Intelligence, Modularity, Mobility, and Experimental Reusability) which has the ability to estimate step count and energy expenditure was also analysed to determine its criterion validity as a measure of physical activity in people with RA. The results of this study determined that SHIMMER worn on the thigh shows promising results as a valid measure of step count in this population. Thus, a SHIMMER was also worn on the thigh for the studies outlined in Chapter 7, 8, 9 and 10. However the ability of the algorithms which are used to determine step count for SHIMMER are, as yet, unable to be utilised for a longer period than the 75 minute protocol and thus could not produce data for habitual free living physical activity as required in Chapter 7, 8, 9 and 10.

The results of this validation study utilising SHIMMER are outlined in Appendix A.
SECTION 2

This section of the thesis encompasses Chapter 6, 7, 8 and 9.

Chapter 6 will describe in detail the methodology used generically in the studies of Chapter 7, 8 and 9, and the decisions made in this regard. In addition, detail on the data reduction procedures which were applied on the SWA output is outlined. Again, the reasoning, embedded in previous research, behind the various decisions made in regard to data reduction has been highlighted.

Chapter 7 stems from the systematic review presented in Chapter 3 and will profile the energy expenditure levels of the RA population and will make reference as to how these levels compare to a control population. This chapter will also identify correlates of energy expenditure in this population.

Chapter 8 stems from the review presented in Chapter 4 and will present the results of an examination, in the RA population, of the relationships between energy expenditure levels and inflammatory marker levels known to be related to cardiovascular disease.

Chapter 9 will describe the results of a study which determines the criterion validity of a frequently utilised subjective measure of physical activity, the International Physical Activity Questionnaire – Short Form (IPAQ-SF), in the RA population.
CHAPTER 6 GENERAL METHODOLOGY
6.1 Ethical Approval

All procedures of the studies outlined in Chapter 7, 8, 9 and 10 were reviewed and approved by the Mid Western Regional Hospital Ethics Review Board, Limerick prior to the beginning of the studies.

6.2 Subject Recruitment

6.2.1 RA Subjects

People with RA attending the rheumatology outpatient clinics in the Mid-Western Regional Hospitals Limerick were eligible for this study.

Inclusion criteria:

- over 18 years of age
- had a diagnosis of RA according to ACR criteria (Arnett et al. 1988)
- could mobilise independently or with assistance of a maximum of one unilateral aid
- were not pregnant

Prior to the clinic beginning, potential subjects’ healthcare records were screened for diagnosis of RA in line with ACR criteria (Arnett et al. 1988) and an age of over eighteen by Marie Tierney. Potential subjects were approached by a member of their healthcare team and it was verbally outlined to them that a study was being undertaken involving individuals with RA. If a potential subject expressed an interest in participating, the study was explained in further detail and criteria for inclusion in the study were assessed by Marie Tierney.

If potential subjects met the inclusion criteria, they were supplied with an information sheet in order to make an informed decision on whether they wished to participate in the study or not. If a subject wished to participate in the study and was willing to return to the clinic for two assessments, this was facilitated. For subjects’ ease (travel and time taken off work etc), if a subject wished to have their initial assessment on the day which the study was introduced to them, this was also facilitated. All subjects provided written informed consent before testing.
79 RA subjects (28 male, 51 female) were recruited to participate in this trial. Four subjects (one male, three female) withdrew from the study without completing the period of monitoring. Reasons for non completion were: illness, family bereavement, family dissatisfaction, and did not provide reason. Of those who completed the seven days of monitoring (n=75), 16 subjects (nine male, seven female) did not achieve a valid week (as defined in section 6.4) and thus their data was not analysed. Thus, analysis was conducted on 59 RA subjects (18 male, 41 female).

**FIGURE 6.1 FLOW DIAGRAM OF RA SUBJECTS RECRUITMENT**

![Flow Diagram](image)

**6.2.2 CONTROL SUBJECTS**

The selection of an appropriate control group is a crucial issue in the conductance of epidemiological studies (Sadetzki et al. 2003). The leading principle is to select controls which will be representative of the general population from which the group under investigation was recruited. Two categories of control subjects have typically been used in studies investigating physical activity in rheumatoid arthritis: other rheumatic controls and healthy controls. It was felt that there were limitations with the utilisation of both of these categories of control populations. Firstly rheumatic
disease controls will have similar disabilities to the RA population and thus potentially experience similar barriers to physical activity as the RA subjects. Furthermore, because of the disabilities indicative of this group, these controls would not be considered representative of the general population. However, the use of a healthy control population also is fraught with limitations. As the variable under consideration in this study is level of physical activity, it was important that both groups would have similar exposure levels to GPs and primary healthcare services. Numerous studies have shown that GPs give health promoting physical activity advice and education in up to one third of consultations and thus patients who have similar exposure levels to GPs will have similar experience of such physical activity promoting advice (Orrow et al. 2012, Eakin et al. 2007, Hinrichs and Brach 2011). As patients diagnosed with a current or chronic disease are more likely to attend GP and primary healthcare services, it was felt that a disease control group would be most representative. Furthermore, in order to ensure that the control group was representative, a disease control population which was free from physical disabilities which may limit the conductance of physical activity was chosen. Thus, patients who attended a dermatology clinic at the same hospital from which the RA sample was recruited was chosen as the control population.

People attending the dermatology outpatient clinics in the Mid-Western Regional Hospitals Limerick were eligible for this study.

Inclusion criteria:

- over 18 years of age
- could mobilise independently or with assistance of a maximum of one unilateral aid
- were not pregnant
- did not have an arthritic condition

Prior to the clinic beginning, control subjects’ healthcare records were screened for presence of an arthritic condition an age of over eighteen by Marie Tierney. Potential subjects were approached by a member of their healthcare team and it was verbally outlined to them that a study was being undertaken involving physical activity. If a potential subject expressed an interest in participating, the study was explained in further detail and criteria for inclusion in the study were assessed by Marie Tierney.
If potential subjects met the inclusion criteria, they were supplied with an information sheet in order to make an informed decision on whether they wished to participate in the study or not. If a subject wished to participate in the study and was willing to return to the clinic for assessment again, this was facilitated. For subjects’ ease (travel and time taken off work etc), if a subject wished to have their assessment on the day which the study was introduced to them, this was also facilitated. All subjects provided written informed consent before testing.

23 controls (nine male, 14 female) were recruited to participate in the trial. Three subjects (three female) withdrew from the study without completing the period of monitoring. Reasons for non completion were: dissatisfaction did not return monitor, did not give reason. One subject (female) did not achieve a valid week (as defined in section 6.4) and as a result her data was not analysed. Thus, analysis was conducted on 19 dermatology (DERM) subjects (nine male, ten female).

**FIGURE 6.2 FLOW DIAGRAM OF DERMATOLOGY SUBJECTS RECRUITMENT**

23 (9M, 14F) control subjects recruited

3 (3F) withdrew without completing period of monitoring

20 (9M, 11F) completed seven day period of monitoring

1 (1F) did not achieve valid week (as outlined in 6.4)

Analysis conducted on 19 (9M, 10F) control subjects
6.3 PROTOCOL FOR USING SWA TO MEASURE ENERGY EXPENDITURE

Based on the validation work outlined in Chapter 5, SWA was found to be a valid measure of energy expenditure in the RA population. Furthermore it has also been shown to be a valid measure in non disabled adult populations (Berntsen et al. 2010, Johannsen et al. 2010, Jakicic et al. 2004, St-Onge et al. 2007).

6.3.1 APPLICATION OF THE SWA

For all subjects, a SenseWear Armband was applied to the right upper arm. Before each subject began the monitoring period, the subject’s details (age, height, weight, gender, handedness and smoking status) were entered into the SWA software programme (InnerView Research Software v6.1, Bodymedia). After completion of the monitoring period, the SWA data was uploaded to the software programme which uses proprietary algorithms developed by the manufacturers to estimate energy expenditure values from the accelerometry, physiological sensors and demographic data.

Subjects were encouraged to wear the monitors for 24hr a day except during water based activities but were informed that if necessary that the monitor could be removed during non-waking hours. Subjects were also shown how to remove the monitor and accurately re-apply after removal and were provided with an information handbook which visually and verbally outlined this process as well as other information regarding the monitors. The handbook was explained to them at the time of application and any queries were answered. Subjects were also provided with a diary which they were asked to complete outlining the times the monitor was removed or re-applied.

6.3.2 MONITORING PERIOD

Subjects were informed that they were to wear the monitor for eight days. In accordance with the findings of Corder et al. (2008) who found behavioural modification caused by the act of being monitored on the initial day of monitoring, the first day of monitoring was discounted entirely and seven full days of monitoring was utilised. All subjects were contacted (with their permission) on three occasions during the week to ensure that they were not experiencing any problems and to remind them to continue to wear the monitor and complete the diary. This contact
was by phone call, text message or email depending on the subject’s preference. All subjects were provided with the contact details of one of the investigators (MT) and were urged to contact her if they had any queries or problems.

6.4 SWA Data Reduction

Data reduction in this context refers to the processes which were undertaken on energy expenditure data produced by SWA to allow for meaningful data to be produced.

Decisions to be made were on what is a valid day for measurement of physical activity, imputation for non-wear time and the number days to include in order to obtain a determination of habitual physical activity.

Much of the research to date which has utilised SWA has requested subjects to wear the monitor for 24 hours (with removal only for water based activities) and have considered a valid day as a day with at least 1,368 minutes of data, after imputation of known activities, which corresponds to 95% of a 24 hour period (Scheers et al. 2012a).

In this study, it was not feasible for individuals to wear the monitors for a “24 hours a day, seven days a week” protocol due to the clinical nature of the subjects and the non-compensatory nature of the study. Furthermore, the unreliable nature of the diary recordings made imputation of known activities unfeasible.

Thus, further decisions with regard to valid days and the inclusion of off-body estimates were made with regard to SWA use in this RA population. The method of data reduction used in this study was carefully chosen based on the limited literature on SWA reduction currently available.

6.4.1 Valid Day and Imputation

A valid day was considered a day with at least 600 minutes of wear time and at least 1,368 minutes of data which could be accounted for by sleep or wear time. This corresponds 95% of the time which can be accounted for.

When data was missing the following approach was taken:
Imputation for sleep time: missing values for sleep were substituted with the constant MET value (0.9) and associated energy expenditure in accordance with the Compendium of Physical Activities (Ainsworth et al. 2000).

All other missing time: where there was up to 72 minutes of missing time which could not be accounted for by sleep, this period was substituted with the average MET and associated energy expenditure for that day. This approach was based on the recent approach taken by Scheers et al. (2012b) and Almeida et al (2011).

6.4.2 Number of Valid Days
A measurement time frame of at least four consecutive valid days was determined as the measurement period for this study. This decision was based on recent study by Almeida et al. (2011) whose aims included determination of the measurement time frame to obtain consistent estimates of daily energy expenditure in RA. Their study findings are reported in Table 6.1. The results of interclass correlation coefficient analyses and multiple linear regressions indicated the use of two consecutive days data were needed to reliably estimate TEE, however the inclusion of further day’s data strengthened this reliability. Monitor wear of two consecutive days represented an ICC of 0.87 and an adjusted $r^2$ value on logistical regression of at least 0.86. The inclusion of three consecutive days data represented an ICC of 0.91 and an adjusted $r^2$ value on logistical regression of at least 0.92, while the inclusion of four consecutive days data corresponded to an ICC of 0.93 and an adjusted $r^2$ value on logistical regression of at least 0.96. Based on these findings, it was decided to include a measurement time frame of at least four consecutive valid days as the measurement period for this study.
When these two decisions regarding determination of a valid day and number of valid days necessary were applied to the data in the study 16 (nine male, seven female) RA subjects and one (one female) control subject were excluded. Five individuals with RA were excluded as they did not have at least four valid days. A further eleven had at least four valid days, however they did not meet the criteria for the four days being in a consecutive order. This left a final sample of 59 RA individuals who had at a minimum of four consecutive valid days of data. The one control subject who was excluded was excluded as although she exceeded the criteria of having at least four valid days, these were not in a consecutive order. Thus, a final sample of 19 people who had at a minimum four consecutive valid days of data was included in the study. The breakdown of the varying number of individuals who had seven, six, five and four consecutive valid days of data is depicted for both populations in Table 6.2.
### TABLE 6.2 BREAKDOWN OF INDIVIDUALS NUMBER OF CONSECUTIVE VALID DAYS

<table>
<thead>
<tr>
<th>Number of consecutive valid days</th>
<th>RA Population</th>
<th>Dermatology Control Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Total number of individuals</td>
<td>59</td>
<td>19</td>
</tr>
</tbody>
</table>

#### 6.4.3 FINAL UNITS OF MEASUREMENT
- **TEE (kcal/day)**
  - A daily TEE was calculated for each subject. Each valid consecutive day was summed and divided by the number of consecutive days for each subject to find the mean daily TEE (measured in kcal/day).
- **REE**
  - REE was calculated used the Mifflin-St Joer equation (as previously outlined in Chapter 2, section 2.5.4) for the control subjects. REE was calculated for the RA subjects using the equations outlined in Metsios et al (2008a).
- **PAEE**
  - PAEE was calculated as TEE – (REE + TEF)

#### 6.5 RECORDING PERIOD
As previously outlined in section 2.9, the time of year in which measurements of physical occur is important as profound differences can be noted in the physical activity levels in summer compared to winter (Sumukadas et al. 2009, Newman et al. 2009, Buchowski et al. 2009, Pivarnik et al. 2003, Cheadle 2006). Thus, physical activity was measured in this population during summer (daylight saving time period) time, which in 2011 ranged from 27th March 2011 to 30th October 2011.
6.6 DEMOGRAPHIC AND DISEASE RELATED VARIABLES

In order to allow for determine the relationship between TEE and PAEE and demographic and disease related variables (Chapter 7), the following variables were recorded for each subject.

6.6.1 DEMOGRAPHIC VARIABLES

The following variables were self reported and recorded:

- Gender
- Handedness
- Smoking status (current smoker/non smoker)
- Employment status (currently employed/not employed)

In addition, the following variables were measured:

- Age (calculated from date of birth to date of initial assessment)
- Height (measured to the nearest cm using a Seca height measure (Birmingham, UK), with shoes removed)
- Weight (measured to the nearest kg using a Salter mechanical scale (Kent, UK), with shoes removed)
- Body mass index (BMI) (calculated according to the formula: body mass (kg) ÷ height squared (m^2))

6.6.2 DISEASE RELATED VARIABLES

- Medication use. Medications were classified by Marie Tierney into use of biologics, use of DMARDs, use of NSAIDs, use of steroids and use of statins. Use of the Monthly Index of Medical Specialities (MIMS) facilitated this process.
- Disease duration (in years) was recorded from medical charts and was confirmed via self report.
- Tender and Swollen Joint Count.
  Joint swelling is defined as a soft tissue swelling which is detected along the margins of the joint (Sokka and Pincus 2005). Bony swelling and deformity of the joint do not constitute joint swelling. Observation and palpation of the joint were used to determine if a joint was swollen. Joint swelling can influence the
range of motion of the joint (Sokka and Pincus 2005, Scott and Houssien 1996) and thus this was useful in determining the presence of swelling. Joint tenderness is considered to be the presence of pain at rest with the application of pressure and is based on the subject’s reaction (Sokka and Pincus 2005). The pressure to elicit tenderness should be exerted by the examiner’s thumb and index finger and be of sufficient strength to cause whitening of the examiner’s nail bed (Scott and Houssien 1996).

Many standardised joint counts are currently used which assess from 28 to 68 joints. The 28 joint count (Fuchs et al. 1989) was utilised in this study and was conducted by Marie Tierney. This incorporates ten proximal interphalangeal joints of the fingers, ten metacarpalphalangeal joints, wrists, elbows and knees. The 28 joint count is easier to apply than the other methods which utilise increased number of joints, however it has been shown to yield as much information (Fuchs et al. 1989).

- **Global Health.** The Visual Assessment Scale (VAS) (De Boer et al. 2004, Fries and Ramey 1997) is a measurement tool which aims to measure a characteristic or attitude that ranges across a continuum of values, in this case the global health of an individual. Subjects were provided with a 100mm vertical line with anchors of “Worst imaginable health state” and “Best imaginable health state” on either end. Subjects rated how their health was by marking the line. The scale was scored to the nearest mm.

- **Disability.** The Health Assessment Questionnaire (HAQ) (Wolfe et al. 1988) is a self report measure of the extent of a patient’s functional ability. It is the most used measure of disability in arthritis. The HAQ-DI (Disability Index) is the version which is most frequently used. HAQ-DI is comprised of 20 questions in eight categories (Dressing and Grooming, Hygiene, Arising, Reach, Eating, Grip, Walking and Common Daily Activities). There are four response options for each question ranging from no difficulty to unable to do, scored 0 – 3. A higher score indicates greater disability. HAQ-DI has test retest correlations from 0.87 – 0.99. Criterion validity has also been demonstrated with correlations between the questionnaire score and task performance from 0.71 to 0.95. Convergent validity has also been demonstrated based on the pattern of correlations with other clinical and laboratory measurements (http://aramis.stanford.edu/HAQ.html).
Joint tenderness, swelling, VAS score and HAQ score were recorded twice: once on the day of monitor application and again on the day of monitor removal. The average scores were calculated as the mean of the two days scores and it is this value which is reported.

- Composite Disease Activity Score: DAS-28. The DAS-28 is a validated (Prevoo et al. 1995) tool for use in RA that is recommended by the European League Against Rheumatism (EULAR) for evaluation of disease activity. It incorporates 28 swollen and tender joint counts, a self determined assessment of the subject’s general health and acute-phase response (ESR or CRP). The DAS-28 is scored as follows:

  DAS-28 (ESR):
  
  $$0.56\sqrt{Tender_{28}} + 0.28\sqrt{Swollen_{28}} + 0.70\ln(ESR) + 0.014(\text{Global Health VAS})$$

  DAS-28(CRP):
  
  $$0.56\sqrt{Tender_{28}} + 0.28\sqrt{Swollen_{28}} + 0.36(CRP + 1) + 0.014(\text{Global Health VAS}) + 0.96$$

Thresholds have been defined to categorise DAS-28 scores. A DAS-28 score of 2.6 equates to disease remission, 2.6 – 3.2 equates to low disease activity, 3.2 – 5.1 equates to moderate disease activity while scores greater than 5.1 equate to high disease activity (Fransen and Van Riel 2005). These thresholds are applicable irrespective of which form of the DAS-28 is utilised. DAS-28 (ESR) is the original and best known form of the DAS-28. DAS-28 (CRP) was developed as it is suggested that it is potentially a more direct measure of inflammation and also because of the differing effects B-cell therapies have upon both of these inflammatory markers. To date, few studies have been performed to validate DAS-28 (CRP) and thus it was decided to utilise the original form in our DAS-28 analysis.
6.7 Inflammatory Blood Markers
Data on inflammatory blood markers was collected for use to determine if a relationship existed between inflammatory blood markers known to be related to cardiovascular disease and energy expenditure in the RA population.

6.7.1 Procedure
Blood samples were drawn from sitting, non-fasting individuals on one occasion at the time and in the location of their initial assessment at the outpatient clinics of the Mid Western Regional Hospitals, Limerick, by nurses trained in phlebotomy. All serum and plasma samples were centrifuged at 1,800 x g at the Dept. of Pathology, Mid Western Regional Hospital, Limerick for 15 minutes in the before analyses.

WBC, ESR, Fibrinogen and CRP samples were analysed, again at the Dept. of Pathology, Mid Western Regional Hospital, Limerick within four hours of being drawn. Serum samples for IL6, IL8, IL10, SAA and TNF-α were obtained and stored at -70°C at the Dept. of Pathology, Mid Western Regional Hospital, Limerick until analyses, which occurred after transportation on dry ice, at the Conway Institute for Bimolecular and Biomedical Research, University College, Dublin. Before analyses the serum samples were thawed on ice and then centrifuged at 2000 x g for five minutes to remove debris.

6.7.2 White Cell Count
Quantitative determination of WBC was tested as part of a full blood count (FBC). This was conducted on EDTA anticoagulated whole blood using an Advia 120/2120 Haematology analyzer (Siemens Healthcare Diagnostics, Marburg, Germany) as per manufacturer’s guidelines.

6.7.3 C Reactive Protein
Particle enhanced immunonephelometry was performed for quantitative determination of the acute phase protein CRP as per manufacturer’s protocol (CardioPhase hsCRP, Siemens Healthcare Diagnostics, Marburg, Germany) on the BN ProSpec System. A limit of detection for CRP was 0.175mg/L.

6.7.4 Fibrinogen
Using plasma sample, fibrinogen protein concentration was assessed with fibrinogen reagent (Diagnostica Stago, Asnières-sur-Seine, France) on Stago STA-R
coagulometer (STA Diagnostica Stago, Asnières-sur-Seine, France) according to manufacturer’s guidelines which specify the Clauss method.

**6.7.5 Erythrocyte Sedimentation Rate**
Whole blood which was collected in a tube containing the anticoagulant Sodium Citrate in the ratio of Sodium Citrate to whole blood of 4NC to 3.5 was used in the analysis of the rate of erythrocyte sedimentation. It was determined using an automated procedure for measuring ESR using Sediplus S 2000 (Sarsteat AG & Co., Nümbrecht, Germany) according to manufacturer’s guidelines. Measured values were converted to Westergren values.

**6.7.6 Interleukin-6 and Interleukin-8**
The pleiotrophic cytokines IL6 and IL8 levels were measured using a sandwich enzyme immunoassay, as per the manufacturer’s protocol (R&D Systems Minneapolis, MN, USA). The absorbance was measured at 450 nm in a microtiter plate spectrophotometer. Standards ranged from 9.375–600 pg/ml for IL6 and from 43.75-2,000 pg/ml for IL8.

**6.7.7 Interleukin-10**
The levels of the cytokine IL10 were measured using a sandwich enzyme immunoassay, as per the manufacturer’s protocol (BioLegend, Inc., San Diego, CA, USA). The absorbance was measured at 450 nm in a microtiter plate spectrophotometer. Standards ranged from 3.9–80,000 pg/ml. The minimum detectable concentration of IL-10 was 2 pg/ml.

**6.7.8 Serum Amyloid A**
The levels of the acute phase protein SAA were measured using a sandwich enzyme immunoassay, as per the manufacturer’s protocol (Biosource, London, U.K.). The absorbance was measured at 450 nm. Standards ranged from 9.4–300 ng/ml. The minimal detectable level of A-SAA was 5 ng/ml.

**6.7.9 Tumor Neurosis Factor - α**
The levels of the pleiotrophic cytokine TNF-α were measured using a MSD single-spot sandwich immunoassay, as per the manufacturer’s protocol (Meso Scale Discovery, Gaithersburg, MD, USA). The electrochemiluminescence was measured using the Sector Imager 2400 Instrument. Standards ranged from 2.4–10,000 pg/ml. The minimum detectable concentration of TNF-α in serum was 0.3 pg/ml.
6.8 **CHOLESTEROL SAMPLE**

Concentration of Total Cholesterol was determined using the CHOL reagent (Carolina Liquid Chemistries, Brea, CA). Analyses were conducted using the Beckman SYNCHRON Clinical Systems (Beckman Coulter Inc., Brea, CA) in accordance with manufacturer’s guidelines. The analytical range for Total Cholesterol was 0.24 – 17.9 mmol/L. This analysis was completed at the Dept. of Pathology, Mid Western Regional Hospital, Limerick.
CHAPTER 7 A PROFILE OF ENERGY EXPENDITURE AND IT’S CORRELATES IN THE RHEUMATOID ARTHRITIS POPULATION AND A COMPARISON WITH DISEASE CONTROLS
7.1 Introduction

In 1995, exercise specialists from the American College of Sports Medicine and Centers for Disease Control (ACSM/CDC) came together to issue a revised public health directive as evidence mounted that the health benefits (largely cardiovascular) associated with formal exercise regimens also occurred with accumulated lifestyle physical activity (Pate et al. 1995). Their most recently revised recommendation is for the accumulation of 30 minutes of moderate-intensity lifestyle physical activity in short segments (ten minute bouts) on most, if not all, days of the week (Haskell et al. 2007). Furthermore, the American College of Rheumatology (ACR) also supports these recommendations for people with RA (Krebs 2003). Thus, it is recommended that individuals with RA should accumulate as much physical activity as those without the disease.

As demonstrated by the systematic review outlined in Chapter 3, further research investigating the levels of physical activity in the RA population and how these levels compare to control populations is necessitated using well designed protocols as definitive conclusion regarding the levels of physical activity among the RA population cannot be made.

Furthermore, physical activity is one of the most modifiable determinations of chronic morbidity and total mortality (Lagerros et al. 2009, Gulsvik et al. 2011). The decision to engage in physical activity ultimately lies solely with the individual (Dishman et al. 1985), however this decision is influenced by a number of factors. Examining the characteristics of those less likely to be physically active has important implications for developing and understanding the initiation and adoption of this behaviour (Eyler 2003a). Understanding the specific factors that correlate with physical activity and that may be targeted by well designed interventions represent a possible method for developing strategies to address those who are least active in the RA population. This is a recognised strategy for increasing physical activity (Baranowski et al. 1998).

Few research studies have been conducted designed specifically to examine the correlates of physical activity behaviour for people with RA (Wilcox et al. 2005). Most of this work has been conducted assessing the psychosocial correlates of
physical activity in this population (Wilcox et al. 2005), with perceived benefits and self efficacy shown as strong predictors of higher physical activity levels. However, the impact of demographic or RA specific health related factors has been less well investigated despite the frequent assessment of demographic factors in other populations (Plotnikoff et al. 2004, Wilcox et al. 2005, Lagerros et al. 2009).

Resultantly, the first aim of this study was to profile energy expenditure levels in the RA population and compare the levels to that of a hospital control population. The second aim of this study was to examine demographic and health related correlates of energy expenditure in the RA population and determine a model which best predicts energy expenditure behaviour in this population.

7.2 Methodology
The methodology as outlined in Chapter 6 was applied for this chapter.

7.3 Data Analysis
All analyses were completed using PASW version 18.0. Level of significance was defined as $p < 0.05$.

Normality was assessed by use of boxplots, histograms, Quantile-Quantile plots and the Shapiro-Wilk or Kolmogorov-Smirnov statistic where appropriate. A number of variables were found to be non normally distributed and thus were transformed to a normal distribution to allow for parametric analyses. As parametric analysis was conducted, in remaining true to the analysis utilised, it was deemed appropriate to report energy expenditure values using the back transformation where necessary. Back transformation was conducted using the exponential or square as appropriate. Thus, where transformations have been used the geometric mean and 95% confidence intervals for energy expenditure variables are reported. For consistency, where transformations have not been used due to the normal distribution of some variables, mean and 95% confidence intervals have also been reported. Demographic variables displayed a normal distribution. Therefore, mean and standard deviations are reported for these variables.
7.3.1 Transformations

7.3.1.1 Profile of Energy Expenditure in RA
For the total RA sample, log transformations were utilised for TEE and TEF. Square root transformations were used to transform PAEE to normal distribution. For the male RA subsample, a log transformation was utilised to transform REE to a normal distribution. For the female RA subsample, log transformations were utilised for PAEE, REE and TEF.

7.3.1.2 Comparison of Energy Expenditure Levels to Controls
For the total sample, TEE, PAEE and TEF were transformed to normal distribution using log transformations. For the male subsample, log transformations were utilised to transform PAEE to a normal distribution. For the female subsample, no transformation was necessary as all energy expenditure variables exhibited normal distributions.

7.3.1.3 Regression Analysis
For the total sample, log transformations were utilised for TEE, disease duration and average tender count. A square root transformation was used to transform PAEE to a normal distribution. Average swollen count was transformed to a normal distribution using a reciprocal (multiplicative inverse) transformation. For the male subsample, disease duration, average tender count, average swollen count and average HAQ score were transformed to a normal distribution using log transformation. For the female subsample, PAEE, disease duration, average tender count and average swollen count were transformed to display a normal distribution using log transformation methods.

7.3.2 Statistical Analysis

7.3.2.1 Profile of Energy Expenditure in RA
Descriptive statistics were used to profile the energy expenditure levels of the RA subjects. For the purpose of profiling, age was grouped into three categories, under 55, 55 – 65 and over 65. DAS-28 score was categorised into remission (<2.6), low disease activity (2.6 – 3.19) and moderate disease activity (3.2 – 5.09). Disease duration was grouped into less than 3.5 years, 3.5 – 12 years and greater than 12
years. Average HAQ score was grouped into less than 0.5, 0.5 – 1.38 and greater than 1.38.

Differences between weekdays and weekend days were assessed using independent t-tests.

**7.3.2.2 Comparison of Energy Expenditure Levels to Controls**
Differences between the RA and dermatology groups in the continuous variables of age, weight, height and BMI were assessed by independent t-tests.

Differences in the categorical variables of gender, smoking status and employment status were assessed by Chi-square test for independence.

Comparison of energy expenditure variables between groups were assessed parametrically by use of independent t-tests.

Furthermore the groups were divided into subsamples based on sex and again independent t-tests were utilised to assess if differences existed in the energy expenditure variables between RA and DERM groups in both male and female subsamples.

**7.3.2.3 Regression Analysis**
In order to determine if a relationship existed between the demographic and RA specific health factors and the amount of energy expended, point biserial correlations were conducted for dichotomous variables and Pearson’s correlation coefficients for continuous variables were conducted for the energy expenditure variables in total and for the male and female subsamples.

The benchmarks for correlations set forth by Cohen (1988) were used whereby $r = 0.10 – 0.29$ was considered small, $r = 0.30 – 0.49$ was considered moderate and $r = 0.50 – 1.0$ was considered strong.

In order to develop a subset of independent variables which best predicted each of the dependent variables statistical (stepwise) multiple regression analyses was utilised. Significant ($p<0.05$) contributors identified through bivariate analyses were introduced into a stepwise multiple linear regression analysis. This allowed for development of a linear regression model for each dependant variables. A $p \leq 0.05$
was set as the criterion for entry to the model. $R^2$, adjusted $r^2$, regression coefficients ($\beta$), 95% CI for $\beta$ and $p$ values were calculated and models of best fit produced.

Multicollinearity was assessed by examination of the patterns of intercorrelations among independent variables and the computed variance inflation factors. In addition, regression diagnostics were performed to verify the models satisfied all regression assumptions. Examination of the residuals scatterplot was conducted to assess the normality of the residuals and standardised residuals exceeding ±3.3 (Tabachnick and Fidell 2007) were considered outliers. None of the assumptions of multiple regression were violated by the current data.

7.4 RESULTS
7.4.1 DEMOGRAPHIC PROFILE
The demographic profile of the RA population and the DERM population in total and for the male and female subsamples are outlined in Tables 7.1 and 7.2. There were no statistically significant differences noted for age, weight, height or BMI between the two groups for the total sample, males or females and no significant differences were noted for gender, smoking status or employment status for the group as a whole.
### TABLE 7.1 DESCRIPTIVE CHARACTERISTICS OF STUDY SUBJECTS

<table>
<thead>
<tr>
<th>Population</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>p value</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA (n=59)</td>
<td>60.10 (11.27)</td>
<td>0.928</td>
<td>58.63 (11.18)</td>
</tr>
<tr>
<td>DERM (n=19)</td>
<td>60.36 (8.91)</td>
<td></td>
<td>65.68 (7.63)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA (n=59)</td>
<td>77.41 (15.90)</td>
<td>0.278</td>
<td>86.89 (11.62)</td>
</tr>
<tr>
<td>DERM (n=19)</td>
<td>82.95 (18.73)</td>
<td></td>
<td>93.67 (20.55)</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA (n=59)</td>
<td>164.47 (8.73)</td>
<td>0.210</td>
<td>172.50 (4.96)</td>
</tr>
<tr>
<td>DERM (n=19)</td>
<td>167.11 (10.28)</td>
<td></td>
<td>175.67 (7.30)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA (n=59)</td>
<td>28.39 (5.05)</td>
<td>0.398</td>
<td>29.23 (3.92)</td>
</tr>
<tr>
<td>DERM (n=19)</td>
<td>29.52 (5.06)</td>
<td></td>
<td>30.21 (6.01)</td>
</tr>
</tbody>
</table>

### TABLE 7.2 SOCIODEMOGRAPHIC PROFILE OF STUDY SUBJECTS

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>RA (n=59)</th>
<th>DERM (n=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30.5%</td>
<td>47.4%</td>
<td></td>
<td>0.286</td>
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<tr>
<td>Female</td>
<td>69.5%</td>
<td>52.6%</td>
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<td></td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>23.7%</td>
<td>21.1%</td>
<td></td>
<td>1.000</td>
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<tr>
<td>Non Smoker</td>
<td>76.3%</td>
<td>78.9%</td>
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<td></td>
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<tr>
<td><strong>Employment Status</strong></td>
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<td></td>
</tr>
<tr>
<td>Employed</td>
<td>28.8%</td>
<td>36.8%</td>
<td></td>
<td>0.709</td>
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<tr>
<td>Not employed</td>
<td>71.2%</td>
<td>63.2%</td>
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</tr>
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</table>
7.4.2 Profile of Energy Expenditure in RA
This section describes the energy expenditure profile of the subjects.

Table 7.3 outlines the energy expenditure profile of RA individuals, with regard to weekdays and weekend days.

The 59 RA subjects expended a total of 653,983.90 kcals over a total of 276 weekdays. This resulted in a mean weekday TEE of 2,294.57 kcal/day (95% CI: 2,228.09 → 2,363.27). They expended a total of 248,662.10 kcals over a total of 111 weekend days. This resulted in a mean weekend day TEE of 2,187.25 kcal/day (95% CI: 2,099.60 → 2,278.79). No statistical significant difference was noted between daily weekday TEE and daily weekend day TEE (p = 0.077).

The 59 RA subjects expended physical activity related energy of 156,652.20 kcals over a total of 276 weekdays. This resulted in a mean weekday PAEE of 449.96 (95% CI: 397.00 → 506.24). They expended physical activity related energy of 51,115.00 kcals over a total of 111 weekend days. This resulted in a mean weekend day PAEE of 364.70 (95% CI: 297.48 → 438.76). No statistical significant difference was noted between daily weekday PAEE and daily weekend day PAEE (p = 0.076).

**TABLE 7.3 ENERGY EXPENDITURE PROFILE FOR WEEKDAYS AND WEEKEND DAYS**

<table>
<thead>
<tr>
<th></th>
<th>Weekdays</th>
<th>Weekend days</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days</td>
<td>276</td>
<td>111</td>
<td>-</td>
</tr>
<tr>
<td>Total TEE (kcals)</td>
<td>653,983.90</td>
<td>248,662.10</td>
<td>-</td>
</tr>
<tr>
<td>Total PAEE (kcals)</td>
<td>156,652.20</td>
<td>51,115.00</td>
<td>-</td>
</tr>
<tr>
<td>Mean TEE (kcal/day)</td>
<td>2,294.57 (95% CI: 2,228.09 → 2,363.27)</td>
<td>2,187.25 (95% CI: 2,099.60 → 2,278.79)</td>
<td>p = 0.077</td>
</tr>
<tr>
<td>Mean PAEE (kcal/day)</td>
<td>449.96 (95%CI) 397.00 → 506.24</td>
<td>364.70 (95%CI) 297.48 → 438.76</td>
<td>p = 0.076</td>
</tr>
</tbody>
</table>
Table 7.4 outlines the energy expenditure profile of the RA subjects when categorised by varying demographic and health related variables. For age, the youngest tertile had the highest mean TEE and PAEE. This was followed by the middle tertile while the oldest tertile had the lowest mean TEE and PAEE levels. Males had higher mean TEE and PAEE than females. Non smokers had higher mean TEE and PAEE than smokers. Those employed had higher mean TEE and PAEE levels than those who were not employed. Those in the tertile with the lowest HAQ scores (those who had lowest levels of self reported disability) had highest mean TEE and PAEE levels. This was followed by those in the middle tertile, while those in the tertile of highest self reported disability as measured by HAQ had the lowest mean TEE and PAEE levels. Those in remission (as defined by DAS-28 scores) had highest mean TEE and PAEE levels, followed by those classed as having low disease activity, while those categorised as having moderate disease activity had lowest mean TEE and PAEE levels.

**TABLE 7.4 ENERGY EXPENDITURE PROFILE OF RA INDIVIDUALS**

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>N</th>
<th>TEE Mean (kcal)</th>
<th>95% CI</th>
<th>PAEE Mean (kcal)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>59</td>
<td>2,266.97</td>
<td>2,136.66 – 2,405.23</td>
<td>449.73</td>
<td>353.26 – 557.83</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Under 55</td>
<td>17</td>
<td>2,533.61</td>
<td>2,271.96 – 2,825.39</td>
<td>558.77</td>
<td>347.90 – 819.36</td>
</tr>
<tr>
<td>55 – 65</td>
<td>23</td>
<td>2,318.56</td>
<td>2,104.01 – 2,554.98</td>
<td>483.56</td>
<td>312.65 – 691.58</td>
</tr>
<tr>
<td>Over 65</td>
<td>19</td>
<td>1,997.00</td>
<td>1,823.84 – 2,186.59</td>
<td>327.00</td>
<td>211.08 – 468.19</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>2,831.25</td>
<td>2,575.25 – 3,087.25</td>
<td>917.68</td>
<td>745.34 – 1,090.02</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>Female</td>
<td>41</td>
<td>2,104.61</td>
<td>1,978.78</td>
<td>245.87</td>
</tr>
<tr>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td>Non Smoker</td>
<td>45</td>
<td>2,334.84</td>
<td>2,177.65</td>
<td>531.51</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Smoker</td>
<td>14</td>
<td>2,061.52</td>
<td>1,850.85</td>
<td>233.11</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment Status</td>
<td>Not Employed</td>
<td>42</td>
<td>2,120.70</td>
<td>1,998.40</td>
<td>327.43</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Employed</td>
<td>17</td>
<td>2,672.85</td>
<td>2,373.69</td>
<td>834.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>&lt; 3.5 years</td>
<td>20</td>
<td>2,352.19</td>
<td>2,077.46</td>
<td>464.44</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.5 – 12 years</td>
<td>21</td>
<td>2,173.51</td>
<td>1,999.60</td>
<td>426.31</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 12 years</td>
<td>18</td>
<td>2,285.18</td>
<td>2,036.12</td>
<td>461.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average HAQ</td>
<td>Less than 0.5</td>
<td>21</td>
<td>2,451.36</td>
<td>2,225.86</td>
<td>655.58</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.5 – 1.38</td>
<td>21</td>
<td>2,312.30</td>
<td>2,064.00</td>
<td>458.53</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Greater than 1.38</td>
<td>17</td>
<td>2,008.21</td>
<td>1,840.51</td>
<td>240.85</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS</td>
<td>Remission</td>
<td>2,565.73</td>
<td>2,272.87</td>
<td>704.43</td>
<td>451.53</td>
</tr>
<tr>
<td>-----------</td>
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<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Low</td>
<td>11</td>
<td>2,395.15</td>
<td>1,987.24</td>
<td>595.88</td>
<td>322.39</td>
</tr>
<tr>
<td>Moderate</td>
<td>36</td>
<td>2,139.01</td>
<td>1,995.20</td>
<td>340.39</td>
<td>242.12</td>
</tr>
</tbody>
</table>

### 7.4.3 Comparison of energy expenditure levels to controls
Table 7.5 shows the mean values for each of the energy expenditure values (TEE, PAEE, REE and TEF) for the RA and DERM samples in total and for male and female subsample.
## TABLE 7.5 COMPARISON OF ENERGY EXPENDITURE VALUES IN RA AND CONTROL POPULATIONS

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>TEE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>2,266.97</td>
<td>2,136.66</td>
<td>0.912</td>
</tr>
<tr>
<td></td>
<td>→ 2,405.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DERM</td>
<td>2,251.83</td>
<td>2,017.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ 2,513.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAEE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>449.73</td>
<td>353.26</td>
<td>0.248</td>
</tr>
<tr>
<td></td>
<td>→ 557.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DERM</td>
<td>517.13</td>
<td>409.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ 652.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>1,559.75</td>
<td>1,504.23</td>
<td>0.367</td>
</tr>
<tr>
<td></td>
<td>→ 1,615.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DERM</td>
<td>1,493.73</td>
<td>1,354.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ 1,633.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>226.69</td>
<td>213.66</td>
<td>0.912</td>
</tr>
<tr>
<td></td>
<td>→ 240.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DERM</td>
<td>225.20</td>
<td>201.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ 251.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* denotes use of geometric mean
**TEE:** There were no statistically significant differences between TEE in the RA group and the DERM group, although the RA group has slightly higher values found in total and for both the male and female subsamples.

**TEF:** There were no statistically significant differences between the two groups in total or for the male or female subsamples.

**PAEE:** Overall, DERM subjects have higher levels than RA subjects. RA male subjects had higher levels than DERM subjects. However these findings are not statistically significant. For female subjects, a statistically significant difference ($p = 0.003$) between the PAEE values of the RA and DERM subjects was found with DERM subjects expending over twice the energy that RA subjects expended.

**REE:** Overall, RA subjects expended more than the DERM subjects. Male DERM subjects expended more than male RA subjects. These were not significant findings however. For the female subsample, RA subjects expended more than DERM subjects, which was a statistically significant finding ($p = 0.002$).

Figure 7.1 displays a visual representation of these findings. Although there was no statistically significant difference between the TEE of the two groups, differences existed in the REE and PAEE values, highlighting the importance of assessing PAEE and not solely TEE when reporting on physical activity levels in the RA population due to the metabolic abnormalities which impact REE.
FIGURE 7.1 TOTAL ENERGY EXPENDITURE BREAKDOWN FOR TOTAL SAMPLE (FIG. 7.1A), MALE SAMPLE (FIG. 7.1B) AND FEMALE SAMPLE (FIG. 7.1C)
7.4.4 Demographic and Health Related Correlates of Energy Expenditure

Table 7.6 shows Pearson’s correlation coefficients between TEE and PAEE in total and for the male and female subsamples individually and the demographic and RA health factors assessed.
<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Gender</th>
<th>BMI</th>
<th>Smoking</th>
<th>Employment</th>
<th>Location</th>
<th>Disease Duration</th>
<th>PAEE</th>
<th>Total</th>
<th>PAEE</th>
<th>Total</th>
<th>TEE</th>
<th>Total</th>
<th>PAEE</th>
<th>Total</th>
<th>TEE</th>
<th>Total</th>
<th>PAEE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>(p value)</td>
<td>r</td>
<td>(p value)</td>
</tr>
<tr>
<td>TEE_total</td>
<td>-0.516</td>
<td>(&lt;0.0001)</td>
<td>-0.610</td>
<td>(&lt;0.0001)</td>
<td>0.358</td>
<td>(0.005)</td>
<td>-0.235</td>
<td>(0.073)</td>
<td>0.465</td>
<td>(&lt;0.0001)</td>
<td>0.067</td>
<td>(0.616)</td>
<td>-0.050</td>
<td>(0.707)</td>
<td>-0.356</td>
<td>(0.012)</td>
<td>-0.325</td>
<td>(0.348)</td>
<td>-0.124</td>
</tr>
<tr>
<td>PAEE_total</td>
<td>-0.325</td>
<td>(0.012)</td>
<td>-0.618</td>
<td>(&lt;0.0001)</td>
<td>-0.013</td>
<td>(0.924)</td>
<td>-0.361</td>
<td>(0.005)</td>
<td>0.533</td>
<td>(&lt;0.0001)</td>
<td>0.088</td>
<td>(0.506)</td>
<td>0.025</td>
<td>(0.849)</td>
<td>-0.435</td>
<td>(0.001)</td>
<td>-0.434</td>
<td>(0.247)</td>
<td>-0.153</td>
</tr>
<tr>
<td>TEE_male</td>
<td>-0.561</td>
<td>(0.015)</td>
<td>-0.503</td>
<td>(0.034)</td>
<td>-0.254</td>
<td>(0.310)</td>
<td>0.599</td>
<td>(0.009)</td>
<td>-0.084</td>
<td>(0.740)</td>
<td>-0.183</td>
<td>(0.467)</td>
<td>-0.306</td>
<td>(0.216)</td>
<td>-0.121</td>
<td>(0.631)</td>
<td>0.019</td>
<td>(0.941)</td>
<td>-0.063</td>
</tr>
<tr>
<td>PAEE_male</td>
<td>-0.391</td>
<td>(0.109)</td>
<td>-0.317</td>
<td>(0.200)</td>
<td>-0.165</td>
<td>(0.513)</td>
<td>0.552</td>
<td>(0.018)</td>
<td>-0.142</td>
<td>(0.574)</td>
<td>-0.111</td>
<td>(0.660)</td>
<td>-0.384</td>
<td>(0.116)</td>
<td>-0.173</td>
<td>(0.493)</td>
<td>-0.029</td>
<td>(0.910)</td>
<td>-0.124</td>
</tr>
<tr>
<td>TEE_female</td>
<td>-0.595</td>
<td>(&lt;0.0001)</td>
<td>-0.303</td>
<td>(0.054)</td>
<td>-0.202</td>
<td>(0.205)</td>
<td>0.346</td>
<td>(0.027)</td>
<td>0.173</td>
<td>(0.278)</td>
<td>-0.092</td>
<td>(0.568)</td>
<td>-0.127</td>
<td>(0.427)</td>
<td>-0.267</td>
<td>(0.092)</td>
<td>-0.114</td>
<td>(0.479)</td>
<td>0.194</td>
</tr>
<tr>
<td>PAEE_female</td>
<td>-0.295</td>
<td>(0.061)</td>
<td>-0.230</td>
<td>(0.147)</td>
<td>-0.418</td>
<td>(0.007)</td>
<td>0.492</td>
<td>(0.001)</td>
<td>0.121</td>
<td>(0.452)</td>
<td>0.060</td>
<td>(0.710)</td>
<td>-0.284</td>
<td>(0.072)</td>
<td>-0.465</td>
<td>(0.002)</td>
<td>-0.178</td>
<td>(0.266)</td>
<td>0.118</td>
</tr>
</tbody>
</table>

**Legend:**
- Large strength correlation
- Moderate strength correlation
- Small strength correlation (p < 0.05)
Table 7.7 outlines the $R^2$, adjusted $R^2$, $\beta$ (regression coefficients), 95% CIs for $\beta$ and $p$ values for TEE and PAEE.

<table>
<thead>
<tr>
<th>TABLE 7.7 MODELS OF BEST FIT FOR ENERGY EXPENDITURE VARIABLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome variable</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>TEE $r^2 = 0.702$</td>
</tr>
<tr>
<td>Adjusted $r^2 = 0.679$</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>PAEE $r^2 = 0.587$</td>
</tr>
<tr>
<td>Adjusted $r^2 = 0.557$</td>
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</tbody>
</table>
7.4.4.1 TEE
The results of bivariate analysis for the total sample and male and female subsamples are shown in table 7.6. Seven variables were significantly correlated with TEE in the total sample. Two variables (age and gender) demonstrated large strength relationships. Four variables (BMI, employment status, DAS-28 score and average HAQ score) showed moderate strength relationships while steroid use showed a small strength relationship.

Of these seven variables, four (gender, age, BMI and employment status) remained significant and were included in the final model (table 7.7). A total of 67.9% of the variance in TEE was explained by the final model.

7.4.4.2 PAEE
The results of bivariate analysis for the total sample and male and female subsamples are shown in table 7.6. Seven variables were significantly correlated with PAEE in the total sample. Two variables (gender and employment status) demonstrated large strength relationships. Four variables (age, smoking status, DAS-28 score and average HAQ score) showed moderate strength relationships. Steroid use showed a small strength relationship with PAEE.

Of these seven variables, four (gender, employment status, smoking status and average HAQ score) remained significant and were included in the final model (table 7.7). A total of 60.5% of the variance in PAEE was explained by the final model.

7.5 DISCUSSION
7.5.1 PROFILE OF ENERGY EXPENDITURE IN RA
The results of this study provide an outline of TEE and PAEE in the RA population and this study adds to the small body of literature in this area.

Furthermore, this study outlines some interesting findings with regard to energy expenditure levels when grouped based on a number of demographic and RA related factors.

This study gives an outline of mean energy expenditure levels based on age, smoking status, employment status, average HAQ score, DAS-28 score and disease duration.
Outlines of energy expenditure in this manner have not previously been conducted in the RA population. Our findings show that energy expenditure is lowered in older age categories, males have higher energy expenditure levels than females, non smokers have higher energy expenditure levels than smokers, employed individuals have higher energy expenditure than non employed individuals, higher energy expenditure levels are found in lower disease activity and severity categories, while no particular pattern of energy expenditure levels were noted dependent on disease duration. These unique findings allow more accurate indication of energy expenditure levels in the RA population.

The results of this study can be compared with some others previously conducted in the area. Roubenoff et al. (2002) measured energy expenditure in its constructs using DLW in the female RA population. They found TEE of 2,181.39 kcal/day. Piva et al. (2010), also in the female RA population found TEE of 2,099 kcal/day when measured using SWA. Hagfors et al. (2005) using DLW in a mixed gender RA population found TEE of 2,569.98 kcal/day. Henchoz et al. (2012) using the physical activity frequency questionnaire, again in a mixed gender RA population found TEE of 2,392 kcal/day. Thus, our study has found similar results. When compared to the female subsample of our study, the Roubenoff et al. (2002) subjects expended 76.77 kcal more per day, while the Piva et al. (2010) subjects expended 5.61 kcal less per day. The Hagfors et al. (2005) subjects expended 303.01 kcal more per day and the Henchoz et al. (2012) subjects expended 125.03 kcal more per day than the total sample of our study.

When the various constructs of energy expenditure are examined, comparing the results of the Roubenoff et al. (2002) study to our female subsample, it can be seen that the TEF levels are relatively similar (217.83 kcal/day compared to 206.95 kcal/day). As previously mentioned, TEE values are also relatively similar (2,181.39 kcal/day compared to 2,104.61 kcal/day). However, Roubenoff et al. (2002) found 1,283.08 kcal/day were attributable to REE, resulting in PAEE of 680.47 kcal/day. In our study, REE was found to be 1,514.14 kcal/day, resulting in a PAEE finding of 245.87 kcal/day. This relates to a 231.06 kcal/day lower REE and a 434.60 kcal/day lower PAEE in our study population.
Roubenoff et al. (2002) utilised indirect calorimetry in their measurement of REE whereas the present study utilised equations specifically designed to estimate REE in the RA population (Metsios et al. 2008a) which have been shown to provide an accurate prediction of REE in RA patients after validation against indirect calorimetry.

Indirect calorimetry is the most accurate measurement of REE, thus the findings of our study may indicate that the new prediction equations designed for specific use in the RA population may not be as accurate as previously thought. Alternatively, as the equations used have been validated against indirect calorimetry in the RA population, it may be that our sample of RA individuals may have a particularly elevated REE rate or the Roubenoff et al. (2002) subjects had a particularly low REE. Metsios et al. (2008a) reported a measured (indirect calorimetry) REE in their mixed gender RA sample of 1,638.30 kcal/day, a 78.55 kcal/day higher rate than our total sample levels. Further studies utilising the prediction equations developed by Metsios et al. (2008a) will allow further inferences to be made on this matter.

Studies have demonstrated varying results with regard to physical activity differences on weekday and weekend days. Buchowski et al. (2004), Miller and Brown (2004) and Tudor-Locke et al. (2004) found increased activity on average weekdays compared to average weekend days, however these differences were found in non disabled populations. Almeida et al. (2011) investigated differences in physical activity behaviour on weekdays and weekend days in the RA population and found no statistically significant difference in activity levels based on the day of the week. Our study found similar results to that of Almeida et al. (2011), with no statistically significant differences noted between weekdays and weekend days. As suggested by Almeida et al. (2011), a potential explanation for this may be related to the fact that the RA population may not utilise the weekend for exercise purposes, which is postulated in the healthy population. They may instead pace themselves, exerting a similar level of energy throughout each day of the week as a means of not further increasing symptoms, in particular fatigue.
7.5.2 COMPARISON OF ENERGY EXPENDITURE LEVELS TO contROls

To our knowledge, this is the first study which has compared energy expenditure in RA compared to non-rheumatic disease controls. The results show that in the female subsample DERM subjects expended statistically significantly more PAEE than RA subjects. Furthermore, statistically significant findings were also found for REE with RA subjects expending significantly more energy than DERM subjects.

The selection of an appropriate control group is a crucial issue in the undertaking of epidemiological studies (Sadetzki et al. 2003). The leading principle is to select controls which will be representative of the general population from which the group under investigation was recruited. The results of studies conducted to date comparing physical activity levels in RA subjects and controls have utilised two types of controls groups for comparison. A number of studies (Mancuso et al. 2007, Roubenoff et al. 2002, Tourinho et al. 2008, Wikstrom et al. 2006) utilised healthy controls, others (Raftery et al. 2009, Greene et al. 2006) utilised controls who had other rheumatic diseases while one study (Lemmey et al. 2001) utilised both healthy and rheumatic disease controls. The results of these studies found that healthy controls were statistically significantly more physically active than RA subjects while there were no statistically significant differences between rheumatic disease controls and RA subjects. However, it was felt that there were limitations with the utilisation of both of these categories of control populations. Firstly rheumatic disease controls will have similar disabilities to the RA population and thus experience similar barriers to physical activity as the RA subjects. Furthermore, because of the disabilities indicative of this group, these controls would not be considered representative of the general population. However, the use of a healthy control population also is fraught with limitations. As the variable under consideration in this study is level of physical activity, it was important that both groups would have similar exposure levels to GPs and primary healthcare services. Numerous studies have shown that GPs give health promoting physical activity advice and education in up to one third of consultations and thus patients who have similar exposure levels to GPs will have similar experience of such physical activity promoting advice (Orrow et al. 2012, Eakin et al. 2007, Hinrichs and Brach 2011). As patients diagnosed with a current or chronic disease are more likely to attend GP and primary healthcare services, it was felt that a disease control group would be
most representative. Furthermore, in order to ensure that the control group was representative, a disease control population which was free from physical disabilities which may limit the conductance of physical activity was chosen. Thus, patients who attended a dermatology clinic at the same hospital from which the RA sample was recruited was chosen as the control population.

The results of this study revealed that there were no statistically significant differences between the RA population and dermatological disease controls in terms of TEE. The results are similar to the results found when comparisons were made with rheumatic disease controls and dissimilar to the results found in studies in which comparisons were made with healthy control populations. It may appear unexpected that RA subjects expend a similar level of energy in total as a non disabled control group which are not limited by symptoms like pain, stiffness and fatigue. However, PAEE is the most modifiable component of TEE and significant differences were found for PAEE for the female subsample where DERM subjects expended statistically significantly more energy related to physical activity than their RA counterparts. Disparate, although not statistically significant findings were found in the male subsample where RA subjects expended more energy related to physical activity than their DERM counterparts. There are a number of factors which may explain, at least in part, some of these findings.

The lowered PAEE values found predominantly and significantly in the female subsample but also in the total sample are to be expected. RA is a chronic disease which commonly results in disability. Research conducted has identified factors such as pain, fatigue, weakness and lack of energy as barriers to physical activity in the RA population (Kamwendo et al. 1999, Wilcox et al. 2006, Der Ananian et al. 2006, van Den Berg et al. 2008). As the DERM population do not experience the disease symptoms as the RA population, these barriers are not applicable and thus, may at least in part, explain the significantly higher PAEE levels in the DERM population. Furthermore, as RA is a condition concomitant with a high metabolic state, REE has been shown to typically be heightened in this population compared to the normative population (Rall and Roubenoff 2004, Roubenoff et al. 1994). REE was found to be statistically significantly higher in the female RA population (as estimated using equations developed specifically for the RA population (Metsios et al. 2008a))
compared to the DERM population (as estimated using the Mifflin-St Joer equation). Thus, the percentage of TEE attributable to PAEE in the RA population is lower in comparison to the DERM population.

The male subsample shows contrasting findings in PAEE levels, with the RA population displaying higher PAEE levels than the DERM population. This is not a statistically significant finding but does deserve some investigation. The male RA subsample in the study had a lower DAS-28 score than the female subsample (2.86 compared with 3.56 respectively). Furthermore, the male subsample had less functional disability than the female subsample. Average HAQ score in males was 0.6 while in the female subsample it was 1.06. These findings may indicate that the males investigated in this study may be representative of a well functioning RA population with disease activity which was extremely low and thus may not be experiencing the same barriers to physical activity as the female subsample. Furthermore, despite not being statistically significant, male DERM subjects were over seven years older than the male RA subjects (65.68 years compared to 58.63 years). As energy expenditure has been shown to decrease with age (Table 7.4), this may also be causative.

There are some issues relating to the measurement tool which was utilised which may have an effect on the results of this study. Although validation studies have been conducted in both the RA and general population, SWA has been shown to have some issues in both populations with regard to the accuracy of energy expenditure values when compared to doubly labelled water and/or calorimetry. SWA tends to overestimate energy expenditure in the RA population (Chapter 5), thus it is likely that the TEE and resultantly PAEE expended by the RA population in the study may be less than has been reported. Conversely, the general consensus from validation work conducted to assess the accuracy of SWA to measure energy expenditure in the general population tends to find that it underestimates TEE and thus PAEE in free living conditions (St-Onge et al. 2007, Berntsen et al. 2010, Johannsen et al. 2010). Therefore, the results of the energy expenditure reported for the dermatology controls may actually be lower than in reality. Thus, it may in fact be the case that the difference found between the RA subjects and dermatology controls for the total
and female subsamples may in fact be larger, while the differences noted in the male subsample may be moderated.

The results of this study highlight the importance of examining PAEE rather than TEE, especially in the RA population, when physical activity is the variable under investigation. Although TEE was quite similar between the two groups for the total sample, male subsample and female subsample with higher levels consistently found for the RA population, differences were noted in REE and thus PAEE, particularly for the female subsample, where statistically significant differences were noted.

7.5.3 CORRELATES OF ENERGY EXPENDITURE IN THE RA POPULATION
The present study examined demographic and health related correlates of objectively measured energy expenditure in the RA population and adds to the small volume of research in this area.

This study found that consistently moderate to strong relationships existed between age, gender, BMI and employment status. Moderate strength relationships were found between PAEE and smoking status, particularly in the female population. Consistently moderate strength relationships were found between DAS-28 score and energy expenditure in the male subsample, but not in the female subsample. Conversely moderate strength relationships were found between HAQ score and energy expenditure in the female, but not the male subsample. Biologic use, DMARD use and steroid use showed less consistent moderate strength relationships with a number of energy expenditure variables

Although, as previously mentioned, there is a lack of research investigating correlates of physical activity in the RA population, some comparisons can be made with our findings and those reported in the literature to date.

In the general and other disease populations, age is typically inversely related to physical activity (Kaplan et al. 2001, Eyler et al. 2002, Zizzi et al. 2006, Coups et al. 2009, Bungum et al. 2011). Lagerros et al. (2009) states that is reasonable to assume this as older age leads to a reduction in everyday activity. In the arthritis population, this inverse relationship also appears to be the case (Semanik et al. 2004, Kaplan et al. 2003), however Greene et al. (2006) found no association between age and physical activity. The results of our study corroborate the predominant findings in
that an inverse relationship appears to exist between energy expenditure and age. The relationship appears stronger for TEE than PAEE.

Gender has also been shown to correlate with physical activity in the general (Kaplan et al. 2001, Zizzi et al. 2006, Zhao et al. 2011) and there is also some evidence in the RA population (Kaplan et al. 2003, Greene et al. 2006), with female having lower levels of physical activity when compared to men. The present study also found this with large strength relationships for TEE and PAEE. However, this would be expected to be the case as the amount of energy that is expended is largely based on the body weight and composition of the individual and as males are typically larger than females (males have 15.8% higher body weight (kg) than females in this sample), this is a likely reason for this finding. Females have consistently been found to be less physically active than males at all life stages (Chad et al. 2005, Hannon 2008, Bauman et al. 2009, King et al. 2011), thus perhaps these findings are not such surprising features.

BMI is a variable which showed moderate and strong strength relationships with the energy expenditure constructs investigated. TEE and PAEE showed positive correlations with BMI. In much of the literature conducted to date (Zizzi et al. 2006, Yang et al. 2012, Bruce et al. 2002, Trost et al. 2002) BMI is typically negatively associated with physical activity, meaning that those of a higher BMI have lower physical activity levels. Kaplan et al. (2003) demonstrated similar results in the arthritis population, in which they found that overweight subjects had higher levels of inactivity as measured by self report leisure time inactivity. Our TEE and PAEE findings are in direct contrast and appear almost counterintuitive. However these contrasting finding can be easily explained as total caloric output is influenced by the total body weight of the subject (Schoeller and Jefford 2002).

Employment status was also found to be a variable which was consistently demonstrated moderate to strong strength relationships with energy expenditure in the current study. Previous research has found both contrasting findings with no definite pattern seen as yet. Individuals who are employed are found to be more physically active (Eyler 2003b, Semanik et al. 2004) but there are also reports showing no association (Evenson et al. 2003, Shibata et al. 2009). In our study, a
moderate to strong strength positive relationship was found between energy expenditure and employment.

Similar to employment, the literature conducted assessing smoking status as a predictor of physical activity and energy expenditure is not fully definitive. Rodriguez-Romo et al. (2010) found that smokers are less likely to meet physical activity recommendations. Kaczynski et al. (2008) conducted a systematic review which found that there is a general negative association but this is often attenuated or reversed in males. Biddle et al. (2005) found that in adolescent girls, smoking is negatively associated with physical activity while the same finding is not found in males indicating that this gender imbalance begins at an early age. Our study also found this gender imbalance in the RA population, where significant correlations were found between female smoking status and energy expenditure which were not found in the male sample.

HAQ scores showed consistent moderate strength relationships with energy expenditure in our study. These moderate strength inverse relationships were displayed only in the total sample and female subsample, indicating that the more disabled a subject, the less energy they expend but interestingly it was a negligible or small strength relationship in the male subsample. Functional limitations were assessed by the Kaplan et al. (2003), Greene et al. (2006) and Eurenius and Stenstrom (2005) studies which assessed the correlates of physical activity in arthritis populations. Greene et al. (2006) and Eurenius and Stenstrom (2005) also used the HAQ while Kaplan et al. (2003) asked subjects whether they had functional limitations or not. Both the Kaplan et al. (2003) and Greene et al. (2006) studies, in line with our study, found that functional limitations were associated with lower physical activity levels. Eurenius and Stenstrom (2005) however, reported the finding of only very low strength relationship between the two variables. Greene et al. (2006) assessed only female samples and Eurenius and Stenstrom (2005) did not assess gender separately and thus reference to gender differences in these studies cannot be made. However Kaplan et al. (2003) assessed gender individually but conversely to the findings of our study, found that presence of functional limitations was a stronger predictor of physical activity in males than females although both were significant at p<0.001.
Disease activity (DAS-28) has not frequently been investigated as a correlate of physical activity in the RA population. Eurenius and Stenstrom (2005) found very low strength correlations between self reported physical activity and DAS scores. This is in direct opposition to the findings of our study in which TEE and PAEE variables demonstrated moderate strength inverse relationships with DAS-28 scores, particularly in the total sample and male subsample, with correlations typically approaching moderate strength in the female population. However, similar to our findings, Munneke et al. (2003) found that low attendance rates in a long term exercise programme in individuals with RA were associated with high mean disease activity as measured by DAS-4. The findings of our study indicate that RA individuals, in particular males with high DAS-28 scores are potentially less likely to expend as much energy as their counterparts with lower DAS-28 scores.

Steroid use was found to show moderate strength inverse relationships with a number of energy expenditure variables, particularly in the female subsample in this study. There does not appear to be previous evidence assessing steroid use as a correlate of physical activity in the RA population. However, as steroid use is typically used in the short term to suppress inflammation and combat acute flares of the disease (Dennison and Cooper 1998), it may be indicative of high disease activity, similar to DAS-28 score results.

The regression models provide us with the best predictors of each of the energy expenditure constructs.

The model of best fit for TEE included the variables gender, age, BMI and employment status. The variables which produced the model of best fit for PAEE included gender, employment, smoking status and average HAQ score.

Gender and employment status were the two most consistent explanatory variables in each of the energy expenditure constructs assessed. Both of these dependent variables appeared in each of the final models. Gender makes a 22.6% and 21.2% unique contribution to TEE and PAEE respectively. Employment status explains 4.5% and 6.5% of the total variance in TEE and PAEE respectively. Thus, gender makes the strongest consistent unique contribution to energy expenditure in the RA population.
The explanatory variables included in our study explained quite a significant amount of the variation in objectively measured energy expenditure. This was in contrast with other evidence. Previous studies which have used objective measures of physical activity have typically explained approximately 20% of the variation in physical activity in their final models (King et al. 2011, Salmon et al. 2003), whereas our final model represented approximately 50% of the variance in each of the energy expenditure constructs under investigation.

Despite displaying moderate strength relationships with each of the energy expenditure constructs in bivariate analyses, DAS-28 scores did not appear in any of the prediction models. This is potentially due to overlap with the other independent variables in the models, despite the assumptions of multicollinearity not being violated.

This cross sectional study cannot infer causation but what this study does provide us with is information regarding how best to develop physical activity type interventions for this population. These findings could help determine which patients have most potential to energy expenditure and thus tailor lifestyle and physical activity programmes and utilise resources most efficiently and effectively. In the present study, some significant correlates of energy expenditure were non-modifiable (age, gender), though some are at least potentially modifiable (BMI, smoking status, employment status, DAS-28 score, average HAQ score, medication usage).

### 7.6 Future Research Recommendations

Further investigation is warranted to determine if the differences noted in energy expenditure levels in the RA and control population are routinely noted, particularly with regard to the differences based on gender noted in the present study.

Further investigation of the Metsios et al. (2008a) equations to measure REE is needed to determine if these equations are appropriate or if utilisation of indirect calorimetry is required to obtain an accurate representation of REE and thus PAEE in the RA population in light of the heightened metabolic state of this population.
Further investigation into potential differences in energy expenditure levels in RA and control populations with age and sex matching is also required. Although there were no statistically significant differences in demographic details of the two populations (Tables 6.1 and 6.2), differences were noted, particularly in relation to age and gender breakdown, of the two populations.

Implementation and evaluation of an intervention with the aim of increasing energy expenditure levels designed using the information presented in the correlates aspect of this study is recommended.

7.7 CONCLUSION

The findings of this study add to the limited research assessing TEE in the RA population. It also adds to the even further limited research assessing PAEE, and appears to be the first to outline energy expenditure levels of male RA subjects. It is also the first to provide details of energy expenditure levels based on various demographic and RA factors.

The findings indicate that TEE levels of individuals with RA appear similar to those reported previously in the literature, although REE and PAEE levels may differ.

The study also is the first to compare energy expenditure levels in the RA population to a non-rheumatic disease population. The findings show TEE was quite similar between the two groups for the total sample, male subsample and female subsample with higher levels consistently found for the RA population. However, differences were noted between the two groups in REE and thus PAEE levels, particularly for the female subsample, where statistically significant differences were noted.

Thus, the results of this study highlight the importance of examining PAEE rather than TEE, especially in the RA population, when physical activity is the variable under investigation.

Furthermore, the present study has identified a number of significant correlates of energy expenditure in the RA population. Age, gender, average HAQ score, DAS-28...
score and employment status were considered important correlates as they were significant across the range of energy expenditure constructs for the total sample.

Prediction models which outline the groupings of variables which best predicted each of the energy expenditure constructs are also presented. Gender and employment status were determined to be the two most consistent explanatory variables in the energy expenditure variables assessed with gender making the strongest unique contribution to energy expenditure in the RA population.

Future interventions aimed at increasing energy expenditure levels in this population group should be informed by evidence of the present study.
CHAPTER 8 THE RELATIONSHIP BETWEEN ENERGY EXPENDITURE AND INFLAMMATORY MARKERS IN THE RHEUMATOID ARTHRITIS POPULATION
8.1 Introduction

It has recently come to light that the increased mortality risk in the RA population is related to increased cardiovascular disease risk. As previously outlined, according to Peters et al. (2010) the key feature explaining the increased cardiovascular risk in this population appears to centre on inflammation although it is likely that traditional cardiovascular risk factors and the side effects of some anti-rheumatic and other drug treatments may also have an impact.

As has been outlined in Chapter 4, in light of the adverse outcomes associated with high inflammatory marker levels, substantial interest exists in indentifying interventions that can reduce the inflammatory burden as measured by markers. Indentifying modifiers of inflammatory marker levels is potentially important in developing appropriate strategies and treatments to minimise the development and impact of CVD. It is reasonable to hypothesise that physical activity may reduce the risk of CVD in the RA population by reducing or preventing inflammation, as this has been shown to be the case by previous research in various populations (Chapter 4). However, when investigating the impact physical activity has on inflammation in the RA population, only a small range of inflammatory markers have been assessed, whereas a larger range has been assessed in the general population. It is necessary to assess additional markers in the RA population to definitively confirm or negate which, if any, inflammatory markers are associated with physical activity in the RA population. Furthermore the use of an objective physical activity measurement tool which has been validated in the RA population would be preferential to limit the impact of reporting bias.

The aim of this study is to investigate if a relationship exists between objectively measured energy expenditure levels and inflammatory markers known to be related to CVD (CRP, ESR, Fibrinogen, IL6, IL8, IL10, SAA, TNF-α and WBC) in the RA population and assess if these relationships persist after adjusting for other factors associated with high levels of inflammatory markers, such as age, BMI, smoking status, disease activity, cholesterol, gender and statin use.
8.2 Methodology

The methodology as outlined in Chapter 6 was applied for this chapter.

Further to this, covariates were chosen to be used based on their independent impact upon levels of inflammatory markers in previous literature (Panagiotakos et al. 2004, Albert et al. 2004, Colbert et al. 2004, Reuben et al. 2003, Verdaet et al. 2004, McDermott et al. 2004, Metsios et al. 2009, Ridker et al. 2005, Albert et al. 2001). The covariates utilised were age, BMI, Cholesterol, DAS-28, Gender, Smoking Status and Statin use.

8.3 Data Analysis

All analyses were completed using PASW version 18.0. Level of significance was defined as $p < 0.05$.

Normality was assessed by use of boxplots, histograms, Quantile-Quantile plots and the Shapiro-Wilk or Kolmogorov-Smirnov statistic where appropriate. A number of variables were found to be non normally distributed and thus were transformed to a normal distribution to allow for parametric analyses. As parametric analysis was conducted, in remaining true to the analysis utilised, it was deemed appropriate to report energy expenditure and inflammatory marker values using the back transformation where necessary. Back transformation was conducted using the exponential, square or reciprocal as appropriate. Thus, where transformations have been used the geometric mean and 95% confidence intervals for energy expenditure and blood marker variables are reported. For consistency, where transformations have not been used due to the normal distribution of some variables, mean and 95% confidence intervals have also been reported.

Demographic variables did not exhibit a non normal distribution. Therefore, mean and standard deviations are reported for these variables.

8.3.1 Transformations

A number of variables were non normally distributed and thus were transformed to allow for parametric analyses. For the total sample log transformations were utilised for CRP, ESR, IL6, IL8, IL10, SAA, and TEE. Square root transformations were
utilised for PAEE. TNF-α was transformed using a reciprocal (multiplicative inverse) transformation. For the male subsample, log transformations were utilised for CRP, ESR, IL6, IL8, IL10 and SAA. A reciprocal transformation was used for TNF-α. For the female subsample, log transformations were utilised for CRP, ESR, IL6, IL8, IL10, SAA and PAEE, while a reciprocal transformation was used for TNF-α.

Where Pearson’s correlation coefficients involving variables transformed using reciprocal methods are presented, the direction of the correlation has been inverted for ease of interpretation.

8.3.2 Statistical Analysis

Bivariate correlation analyses (Pearson’s correlation coefficient) were utilised to assess the strength and direction of the relationship between each of the energy expenditure variables and each of the inflammatory markers. This was conducted for the total sample and both the male and female subsamples.

The benchmarks for correlations set forth by Cohen (Cohen 1988) were used whereby $r = 0.10 – 0.29$ was considered small, $r = 0.30 – 0.49$ was considered moderate and $r = 0.50 – 1.0$ was considered strong.

It is recognised that a number of factors are known to impact on inflammatory marker levels and thus it was assessed whether the energy expenditure variables were statistically significantly contributing to the inflammatory marker levels after the effects of these covariates were accounted for. This was analysed using hierarchical multiple regression. Due to the sample size, these analyses were conducted only on the total sample. Also due to the sample size, limitations were placed on the number of covariates included into the models. Tabachnick and Fidell (2007) recommend a sample size of $N \geq 50 + 8m$ (where $m$ is the number of independent variables). Preliminary analyses were conducted to ensure that the assumptions of normality, linearity, multicollinearity and homoscedasticity were met.

Model 1 adjusted for age, BMI and smoking status. Model 2 adjusted for age, BMI, DAS and Smoking Status. Model 3 adjusted for age, BMI, Cholestrol, DAS, Gender and Smoking Status. Statin use was also included as a covariate for CRP analyses as it has been shown that statin therapy lowers CRP independent of its impact upon cholesterol levels (Ridker et al. 2005, Albert et al. 2001). Covariates were entered in
the first block of hierarchical regression analysis while the energy expenditure variables were entered in the second block of the regression analysis.

For all analyses statistical significance was set at a level of \( p < 0.05 \).

### 8.4 Results

Characteristics of the study subjects are presented in Table 8.1.

**TABLE 8.1 DESCRIPTIVE CHARACTERISTICS OF STUDY SUBJECTS**

<table>
<thead>
<tr>
<th></th>
<th>Total (n=59) mean (SD or 95%CI)</th>
<th>Male (n=18) mean (SD or 95%CI)</th>
<th>Female (n=41) mean (SD or 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.10 (11.27)</td>
<td>58.63 (11.18)</td>
<td>60.74 (11.38)</td>
</tr>
<tr>
<td>Weight</td>
<td>77.41 (15.90)</td>
<td>86.89 (11.62)</td>
<td>73.24 (15.84)</td>
</tr>
<tr>
<td>Height</td>
<td>164.47 (8.73)</td>
<td>172.50 (4.96)</td>
<td>160.95 (7.64)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.39 (5.05)</td>
<td>29.23 (3.92)</td>
<td>28.02 (5.48)</td>
</tr>
<tr>
<td>TEE</td>
<td>2,266.97* (2,136.66 → 2,405.23)</td>
<td>2,831.25 (2,575.25 → 3,087.25)</td>
<td>2,104.61 (1,978.78 → 2,230.43)</td>
</tr>
<tr>
<td>PAEE</td>
<td>449.73* (353.26 → 557.83)</td>
<td>917.68 (745.34 → 1090.02)</td>
<td>245.87* (181.27 → 333.45)</td>
</tr>
<tr>
<td>DAS</td>
<td>3.35 (3.10 → 3.60)</td>
<td>2.86 (2.33 → 3.39)</td>
<td>3.56 (3.30 → 3.83)</td>
</tr>
<tr>
<td>Average HAQ</td>
<td>0.95 (0.76 → 1.15)</td>
<td>0.60* (0.33 → 0.92)</td>
<td>1.06 (0.82 → 1.31)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5.28 (5.01 → 5.55)</td>
<td>5.06 (4.54 → 5.58)</td>
<td>5.37 (5.04 → 5.70)</td>
</tr>
<tr>
<td>CRP</td>
<td>4.31* (3.37 → 5.52)</td>
<td>3.16* (2.10 → 4.78)</td>
<td>4.94* (3.64 → 6.71)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.76 (3.55 → 3.97)</td>
<td>3.55 (3.15 → 3.96)</td>
<td>3.86 (3.61 → 4.11)</td>
</tr>
<tr>
<td>IL6</td>
<td>5.05* (3.13 → 7.86)</td>
<td>6.20* (1.93 → 16.68)</td>
<td>4.60* (2.72 → 7.45)</td>
</tr>
<tr>
<td>IL8</td>
<td>179.94* (128.02 → 252.90)</td>
<td>170.02* (82.99 → 348.28)</td>
<td>184.47* (123.93 → 274.57)</td>
</tr>
<tr>
<td>IL10</td>
<td>8.60* (7.19 → 10.29)</td>
<td>8.46* (6.31 → 11.34)</td>
<td>8.67* (6.87 → 10.92)</td>
</tr>
</tbody>
</table>
Bivariate correlational analysis (Pearson’s correlation coefficient) shows that, for the total sample, energy expenditure variables showed moderate strength relationships with CRP, ESR, Fibrinogen, SAA and WBC with inverse relationships found. These findings are presented in Table 8.2.

More specifically a moderate strength relationship was found between CRP and PAEE (r = -0.447, p < 0.001). Moderate strength correlations were found between TEE and PAEE and ESR (TEE: r = -0.464, p < 0.001; PAEE: r = -0.490, p < 0.001). Fibrinogen showed moderate inverse strength correlations with PAEE (r = -0.316, p = 0.019). SAA demonstrated moderate inverse strength relationships with PAEE (r = -0.322, p = 0.013). WBC showed a moderate strength correlation with PAEE (r = -0.347, p = 0.007).

There were no moderate or large strength correlations found between any of the energy expenditure variables and the inflammatory markers of IL6, IL8, IL10 or TNF-α.

The sample was stratified into male (n=18) and female (n=41) subsamples. Moderate strength correlations were noted between energy expenditure variables and ESR, IL6 and IL8 in the male subsample (Table 8.3). Moderate and large strength relationships were noted between energy expenditure variables and CRP, ESR, Fibrinogen, IL6 and WBC in the female subsample (Table 8.4). Furthermore, it should be noted that in this male subsample, positive relationships were found for CRP, IL6 and IL8.
### TABLE 8.2 TOTAL GROUP CORRELATIONS BETWEEN ENERGY EXPENDITURE VARIABLES AND INFLAMMATORY MARKERS (RECIPROCAL TRANSFORMATIONS ACCOUNTED FOR)

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>ESR</th>
<th>Fibrinogen</th>
<th>IL6</th>
<th>IL8</th>
<th>IL10</th>
<th>SAA</th>
<th>TNF-α</th>
<th>WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>r = -0.176</td>
<td>r = -0.464</td>
<td>r = -0.126</td>
<td>r = -0.065</td>
<td>r = 0.018</td>
<td>r = -0.216</td>
<td>r = -0.243</td>
<td>r = -0.056</td>
<td>r = -0.208</td>
</tr>
<tr>
<td></td>
<td>p = 0.183</td>
<td>p &lt; 0.001</td>
<td>p = 0.360</td>
<td>p = 0.626</td>
<td>p = 0.892</td>
<td>p = 0.101</td>
<td>p = 0.064</td>
<td>p = 0.673</td>
<td>p = 0.115</td>
</tr>
<tr>
<td>PAEE</td>
<td>r = -0.447</td>
<td>r = -0.490</td>
<td>r = -0.316</td>
<td>r = 0.028</td>
<td>r = 0.050</td>
<td>r = -0.186</td>
<td>r = -0.322</td>
<td>r = -0.124</td>
<td>r = -0.347</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.019</td>
<td>p = 0.832</td>
<td>p = 0.709</td>
<td>p = 0.160</td>
<td>p = 0.013</td>
<td>p = 0.350</td>
<td>p = 0.007</td>
</tr>
</tbody>
</table>

### TABLE 8.3 MALE GROUP CORRELATIONS BETWEEN ENERGY EXPENDITURE VARIABLES AND INFLAMMATORY MARKERS (RECIPROCAL TRANSFORMATIONS ACCOUNTED FOR)

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>ESR</th>
<th>Fibrinogen</th>
<th>IL6</th>
<th>IL8</th>
<th>IL10</th>
<th>SAA</th>
<th>TNF-α</th>
<th>WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>r = 0.282</td>
<td>r = -0.334</td>
<td>r = 0.043</td>
<td>r = 0.242</td>
<td>r = 0.242</td>
<td>r = -0.157</td>
<td>r = -0.014</td>
<td>r = 0.052</td>
<td>r = 0.079</td>
</tr>
<tr>
<td></td>
<td>p = 0.257</td>
<td>p = 0.175</td>
<td>p = 0.871</td>
<td>p = 0.334</td>
<td>p = 0.334</td>
<td>p = 0.533</td>
<td>p = 0.957</td>
<td>p = 0.838</td>
<td>p = 0.754</td>
</tr>
<tr>
<td>PAEE</td>
<td>r = 0.147</td>
<td>r = -0.368</td>
<td>r = -0.041</td>
<td>r = 0.358</td>
<td>r = 0.358</td>
<td>r = -0.190</td>
<td>r = -0.083</td>
<td>r = 0.045</td>
<td>r = 0.134</td>
</tr>
<tr>
<td></td>
<td>p = 0.559</td>
<td>p = 0.133</td>
<td>p = 0.876</td>
<td>p = 0.145</td>
<td>p = 0.145</td>
<td>p = 0.451</td>
<td>p = 0.744</td>
<td>p = 0.859</td>
<td>p = 0.595</td>
</tr>
</tbody>
</table>

### TABLE 8.4 FEMALE GROUP CORRELATIONS BETWEEN ENERGY EXPENDITURE VARIABLES AND INFLAMMATORY MARKERS (RECIPROCAL TRANSFORMATIONS ACCOUNTED FOR)

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>ESR</th>
<th>Fibrinogen</th>
<th>IL6</th>
<th>IL8</th>
<th>IL10</th>
<th>SAA</th>
<th>TNF-α</th>
<th>WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>r = -0.207</td>
<td>r = -0.332</td>
<td>r = -0.036</td>
<td>r = -0.371</td>
<td>r = -0.049</td>
<td>r = -0.288</td>
<td>r = -0.233</td>
<td>r = 0.082</td>
<td>r = -0.159</td>
</tr>
<tr>
<td></td>
<td>p = 0.195</td>
<td>p = 0.034</td>
<td>p = 0.830</td>
<td>p = 0.017</td>
<td>p = 0.759</td>
<td>p = 0.068</td>
<td>p = 0.143</td>
<td>p = 0.610</td>
<td>p = 0.322</td>
</tr>
<tr>
<td>PAEE</td>
<td>r = -0.522</td>
<td>r = -0.339</td>
<td>r = -0.327</td>
<td>r = -0.121</td>
<td>r = 0.094</td>
<td>r = -0.280</td>
<td>r = -0.214</td>
<td>r = -0.027</td>
<td>r = -0.318</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p = 0.030</td>
<td>p = 0.045</td>
<td>p = 0.453</td>
<td>p = 0.743</td>
<td>p = 0.192</td>
<td>p = 0.179</td>
<td>p = 0.869</td>
<td>p = 0.043</td>
</tr>
</tbody>
</table>

- **Large strength correlation**
- **Moderate strength correlation**
8.4.2 Multivariate Analysis
In multiple regression analysis accounting for a number of variables which are known to impact upon inflammatory markers based on previous research, a number of the energy expenditure variables made unique statistical significant contributions to inflammatory markers after controlling for these covariates. This is displayed in Table 8.5.
<table>
<thead>
<tr>
<th>Inflammatory marker</th>
<th>Energy expenditure variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$r^2$ change = 0.006</td>
<td>$r^2$ change = 0.003</td>
<td>$r^2$ change = 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.047</td>
<td>Model $p$ value = 0.085</td>
<td>Model $p$ value = 0.063</td>
</tr>
<tr>
<td>CRP</td>
<td>TEE</td>
<td>$r^2$ change = 0.098</td>
<td>$r^2$ change = 0.097</td>
<td>$r^2$ change = 0.086</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.003</td>
<td>Model $p$ value = 0.006</td>
<td>Model $p$ value = 0.007</td>
</tr>
<tr>
<td></td>
<td>PAEE</td>
<td>$r^2$ change = 0.121</td>
<td>$r^2$ change = 0.030</td>
<td>$r^2$ change = 0.010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.007</td>
<td>Model $p$ value = &lt;0.0001</td>
<td>Model $p$ value = 0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$r^2$ change = 0.155</td>
<td>$r^2$ change = 0.048</td>
<td>$r^2$ change = 0.026</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.003</td>
<td>Model $p$ value = &lt;0.0001</td>
<td>Model $p$ value = 0.001</td>
</tr>
<tr>
<td>ESR</td>
<td>TEE</td>
<td>$r^2$ change = 0.002</td>
<td>$r^2$ change = 0.005</td>
<td>$r^2$ change = 0.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.226</td>
<td>Model $p$ value = 0.089</td>
<td>Model $p$ value = 0.149</td>
</tr>
<tr>
<td></td>
<td>PAEE</td>
<td>$r^2$ change = 0.038</td>
<td>$r^2$ change = 0.009</td>
<td>$r^2$ change = 0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.102</td>
<td>Model $p$ value = 0.081</td>
<td>Model $p$ value = 0.211</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>TEE</td>
<td>$r^2$ change = 0.044</td>
<td>$r^2$ change = 0.033</td>
<td>$r^2$ change = 0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.035</td>
<td>Model $p$ value = 0.067</td>
<td>Model $p$ value = 0.148</td>
</tr>
<tr>
<td></td>
<td>PAEE</td>
<td>$r^2$ change = 0.082</td>
<td>$r^2$ change = 0.072</td>
<td>$r^2$ change = 0.039</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.011</td>
<td>Model $p$ value = 0.024</td>
<td>Model $p$ value = 0.074</td>
</tr>
<tr>
<td>SAA</td>
<td>TEE</td>
<td>$r^2$ change = 0.005</td>
<td>$r^2$ change = 0.002</td>
<td>$r^2$ change = 0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.002</td>
<td>Model $p$ value = 0.004</td>
<td>Model $p$ value = 0.001</td>
</tr>
<tr>
<td></td>
<td>PAEE</td>
<td>$r^2$ change = 0.015</td>
<td>$r^2$ change = 0.011</td>
<td>$r^2$ change &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.001</td>
<td>Model $p$ value = 0.003</td>
<td>Model $p$ value = 0.002</td>
</tr>
<tr>
<td>WBC</td>
<td>TEE</td>
<td>$r^2$ change = 0.005</td>
<td>$r^2$ change = 0.002</td>
<td>$r^2$ change = 0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.002</td>
<td>Model $p$ value = 0.004</td>
<td>Model $p$ value = 0.001</td>
</tr>
<tr>
<td></td>
<td>PAEE</td>
<td>$r^2$ change = 0.015</td>
<td>$r^2$ change = 0.011</td>
<td>$r^2$ change &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model $p$ value = 0.001</td>
<td>Model $p$ value = 0.003</td>
<td>Model $p$ value = 0.002</td>
</tr>
</tbody>
</table>
8.4.2.1 Model 1 (Age, BMI and Smoking controlled for)

**CRP:** PAEE made a unique statistically significant ($\beta = -0.366$, $p = 0.010$) contribution and accounted for a 9.8% contribution to CRP.

**ESR:** TEE and PAEE made unique statistically significant ($\beta = -0.466$, $p = 0.005$; $\beta = -0.460$, $p = 0.001$) contributions with TEE making a 12.1% unique contribution and PAEE making a 15.5% unique contribution.

**Fibrinogen:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

**SAA:** PAEE made a unique statistically significant ($\beta = -0.335$, $p = 0.021$) contribution after controlling for the covariates included in this model and accounted for an 8.2% unique contribution.

**WBC:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

8.4.2.2 Model 2 (Age, BMI, DAS and Smoking controlled for)

**CRP:** PAEE made a unique statistically significant ($\beta = -0.403$, $p = 0.011$) contribution and accounted for a 9.7% contribution.

**ESR:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

**Fibrinogen:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

**SAA:** PAEE made a unique statistically significant ($\beta = -0.346$, $p = 0.032$) contribution after controlling for the covariates and made a 7.2% unique contribution.

**WBC:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.
8.4.2.3 Model 3 (Age, BMI, Cholesterol, DAS-28, Gender, Smoking (and Statin Use for CRP only) controlled for)

**CRP:** PAEE made a unique statistically significant ($\beta = -0.480$, $p = 0.015$) contribution, accounting for an 8.6% contribution.

**ESR:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

**Fibrinogen:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

**SAA:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

**WBC:** No energy expenditure variable made unique statistical significant contributions after controlling for the covariates included.

Similar to bivariate correlational analyses, for IL6, IL8, IL10 and TNF-α no energy expenditure variable made unique statistically significant contributions to these inflammatory markers after controlling for the covariates included in model 1, 2 or 3.

8.5 Discussion

The results of this novel study demonstrate some interesting findings in the investigation into the relationship between inflammatory markers and energy expenditure in RA. This study has shown inverse moderate to strong relationships between energy expenditure variables and CRP, ESR, Fibrinogen, SAA and WBC, with some of these relationships existing after controlling for other factors associated with inflammatory markers. Despite demonstrating relationships with physical activity in other populations, the inflammatory markers of IL6, IL8, IL10 and TNF-α did not typically demonstrate significant relationships with energy expenditure variables in the RA population.

A variety of inflammatory markers have previously been investigated in the general population (Geffken et al. 2001, Reuben et al. 2003, Colbert et al. 2004, Verdaet et al. 2004, Pitsavos et al. 2003, Panagiotakos et al. 2005, Borodulin et al. 2006, Dixon
et al. 2009, Autenrieth et al. 2009) with relationships with physical activity found for markers such as CRP, ESR, Fibrinogen, IL6, IL8, IL10, SAA, TNF-α and WBC. Only a limited number of such inflammatory markers (CRP, ESR and fibrinogen) have been investigated in the RA population (Elkan et al. 2011, Metsios et al. 2009).

The results of this study show moderate to strong strength relationships between physical activity and CRP, ESR, Fibrinogen, SAA and WBC in bivariate analysis, between physical activity and CRP, ESR and SAA in multivariate analysis but no significant relationships between physical activity and IL6, IL8, IL10 or TNF-α in any analyses for the total sample.

The reasoning as to why some markers displayed relationships with energy expenditure while others did not may potentially be explained by examination of the individual processes which contribute to the inflammatory cascade. Cytokines such as IL6, IL10, TNF-α and the chemokine IL8 are expressed initially in the inflammatory cascade (Heinrich et al. 1990) with transcription factors such as C/EBPβ (cytidine-cytidine-adenosine-adenosine-thymidine enhancer binding protein beta), AP-1 (activator protein 1) and in particular, NF-κβ (Nucleur Factor-Kappa Beta) implicated in their expression (Firestein 2003, Georganas et al. 2000, Tak and Firestein 2001). As there appeared to be no relationship between energy expenditure and these inflammatory markers, this may indicate that physical activity is not involved in the neutralisation of these markers or the transcription factors involved in their expression.

SAA, CRP and Fibrinogen are involved in the next phase of the inflammatory cascade and are titled the acute phase proteins/reactants. Changes in the concentrations of these acute phase proteins are largely due to changes in their production by hepatocytes (Epstein et al. 1999, Gabay 2006). This is generally in response to circulating inflammatory associated cytokines, however, Bermudez et al. (2002) has previously suggested that circulating concentrations of cytokines and acute phase proteins may not always track one another and independent pathways may also exist. As outlined in Chapter 4, the acute phase proteins, in conjunction with influence from the bone marrow and immune systems systemic reaction result
in leukocytosis, complement activation and an increase in erythrocyte sedimentation rate.

The inverse relationships seen in this study between physical activity and SAA, CRP and Fibrinogen as well as ESR and WBC indicates that physical activity appears to have a moderating impact on these inflammatory markers. It may be that physical activity only has an influence later in the inflammatory cascade in RA, despite having an impact at all phases in the general population and impacting upon both cytokines and acute phase reactants as well as white cell count and ESR. As the mechanism of how physical activity influences inflammation remains unclear (Bruunsgaard 2005, Woods et al. 2009), it is difficult to decipher why this may be the case. Furthermore, the higher degree of inflammation evident in the RA population as well as the autoimmune nature of this inflammation may also play a role in a differing mechanism of how physical activity is impacting upon inflammation in this unique population (Tierney et al. 2012a).

These results also demonstrate that PAEE correlates more closely with inflammatory marker levels than TEE. This implies that the physical activity component is the component most closely related to inflammatory marker levels and consequently physical activity may be expected to significantly and positively impact upon cardiovascular disease risk.

Another interesting finding of this study is the finding that females show a greater number of moderate strength (or greater) bivariate correlations between the energy expenditure variables and the assessed inflammatory markers than the males. This finding has not typically been reported in previous studies on this topic. Notably, the mean values of the majority of the inflammatory markers were higher for the female subsample than the male subsample (Table 8.1) and this was significant for ESR and WBC. It may be that because females have higher inflammatory marker levels, there is greater scope for attenuation by physical activity in this subsample. Furthermore, the female subsample was larger (n=41) than the male subsample (n=18) and so perhaps if the male subsample was larger, significant findings may be found. This difference between male and females be may also be a finding linked specifically to RA population and it may be that in this population, inflammatory markers may be
less sensitive to change by physical activity in the male compared to female subsample.

8.6 Strengths
Firstly, the use of a validated and objective measurement tool for the assessment of TEE and PAEE was used in this study. Predominantly (Geffken et al. 2001, Reubén et al. 2003, Colbert et al. 2004, Autenrieth et al. 2009, Yates et al. 2008, Pitsavos et al. 2003, Panagiotakos et al. 2005, Borodulin et al. 2006, Verdaet et al. 2004), subjective tools, many which only assess particular aspects of physical activity (such as leisure time or sports related physical activity) (Pitsavos et al. 2003, Panagiotakos et al. 2005, Borodulin et al. 2006, Verdaet et al. 2004) have been used. The use of objective measures are unlikely to produce biased results in contrast to subjective methods (Reilly et al. 2008). Secondly, despite the higher cardiovascular risk related to the inflammatory nature of the disease course in RA, this is among the first studies to assess the impact of physical activity as a modulator of inflammatory markers in the population and furthermore, to the authors’ knowledge, it is the only to assess such a wide range of inflammatory markers.

8.7 Limitations
Firstly, the study’s multivariate analyses was limited due to the numbers included in the study and the recommendations of Tabachnick and Fidell (2007). Secondly, similar to the other studies conducted in this area, due to the cross sectional nature of the design of our study, a cause and effect relationship cannot be inferred between physical activity and inflammation. Thirdly, the sample size of our study (n=59) was relatively small when compared to other studies in the area.

8.8 Future Research
Although this study’s findings suggest that a relationship appears to exist between physical activity and inflammatory markers and thus CVD risk in rheumatoid arthritis, further work is needed to confirm this.
Firstly, larger scale, prospectively designed studies are necessary to determine cause and effect between physical activity and inflammatory markers which could not be ascertained in this study due to its design. Secondly, larger scale clinical trials will also be necessary to determine the effect of reduction of inflammatory markers on the risk of CVD mortality. Future research will also be needed to assess the impact of a physical activity programme on inflammatory markers levels and determine the response time between beginning a programme and reduction in inflammatory markers as well as the most appropriate intensity, frequency, type and duration of such a programme.

**8.9 CONCLUSION**

Our study shows that generally moderate strength inverse relationships exist between energy expenditure and CRP, ESR, Fibrinogen, SAA and WBC in bivariate analyses and between energy expenditure CRP, ESR and SAA after controlling for variables known to be associated with inflammatory markers. As these inflammatory markers are associated with an increased cardiovascular disease risk, our study indicates that there may be a relationship between energy expenditure and cardiovascular disease in RA. Our findings emphasise the importance of physical activity in the prevention of CVD through the reduction of inflammatory indices in the RA population. As a result, there should be an increased focus on informing and encouraging individuals in this population regarding physical activity for it not only improves physical function, but can also impede inflammation, and consequently potentially the development of CVD.
CHAPTER 9 CRITERION VALIDITY OF THE INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ) FOR USE IN THE RA POPULATION: COMPARISON WITH THE SENSEWEAR ARMBAND
9.1 INTRODUCTION

Objective methods of physical activity measurement including doubly labelled water (DLW), calorimetry, accelerometers and pedometers are believed to offer more precise estimates of physical activity and remove many of the issues of recall and response bias associated with self report measures, such as questionnaires and diaries (Prince et al. 2008). Despite the advantages of using objective measures, these types of measures are often time and cost intensive and more intrusive rendering them difficult to apply to large epidemiologic settings. Subjective measures, on the other hand, are easier to apply because of their low cost and ease of administration.

The International Physical Activity Questionnaire (IPAQ) is one such self report questionnaire currently in use. Research conducted has reported that the short form last 7 day recall IPAQ (IPAQ-SF) is the recommended format for use (Craig et al. 2003). The IPAQ-SF incorporates four questions and produces a physical activity score based on the previous seven days in MET-hrs. The IPAQ is currently frequently utilised in a variety of populations including the RA population (Metsios et al. 2007, Eppeland et al. 2009, Elkan et al. 2009, Metsios et al. 2009). However the IPAQ has not been validated for use in the RA population, despite its frequent use to measure self-report PA in people with RA.

Measurement validity relates to the extent to which an instrument measures what it is intended to measure (Sim and Arnell 1993). Criterion validity is obtained by comparing the measurements obtained by the tool under investigation with a measureable criterion that is accepted as a standard indicator of a concept or variable (Sim and Arnell 1993). If the instrument gives an accurate representation of the variable, criterion validity has been demonstrated. Concurrent validity is a variety of criterion validity and is concerned with measurements that are obtained at the same time or for the same time period.

A common analysis method used to demonstrate questionnaire validity is to correlate self reported activity data from the IPAQ-SF with data from objective measurement devices(s), both of which are obtained over exactly the same time period. Another common method is to compute the absolute differences between the objective and self report measures.
To evaluate their criterion validity, questionnaires can be compared to physical activity output from objective methods. Compared to use of DLW, the use of accelerometers have the advantage of being a cheaper, simpler and less invasive technique and thus, can be an objective criterion by which questionnaires can be compared.

The aim of this study is to examine the criterion validity of the IPAQ-SF for use in the RA population both by assessing the overall scale, a specific range of activity intensity levels and the absolute differences when compared to the objective criterion measure, Sense Wear Armband (SWA). SWA has already been shown to provide valid data about energy expenditure in the RA population (Tierney et al. In press) and thus is a valid objective tool with which to compare the IPAQ.

9.2 Methodology
9.2.1 General Methodology
A subsample of the total sample (n = 79) were recruited to participate in the current study.

25 subjects (ten male, 15 female) were recruited to participate in this trial. Three subjects did not achieve a valid week of SWA data (as outlined in section 6.4) and thus 22 subjects (eight male, 14 female) participated in this study.

The methodology as outlined in Chapter 6 was applied for this chapter.

9.2.2 International Physical Activity Questionnaire (IPAQ) – Short Form
This questionnaire consists of four questions asking individuals to recall aspects of their physical activity behaviours over the previous seven days. The IPAQ encompasses the amount of time spent sitting, walking and participating in moderate and vigorous intensity activities. Detailed descriptions including concrete examples were given for vigorous and moderate intensity activities.

Guidelines have been developed for data cleansing to account in inaccuracies in the questionnaire completion by individuals (www.ipaq.ki.se/scoring). No inaccuracies were noted in this sample and thus no data cleansing was required.
As recommended by the questionnaire’s developers and in accordance with Craig et al. (2003) and Ainsworth et al. (2000), the frequency and duration of each physical activity category was multiplied by an appropriate MET level to produce a MET-min per week value. The following values are used for the analysis of IPAQ data: Walking: 3.3 METs, Moderate intensity physical activity: 4.0 METs, Vigorous intensity physical activity: 8.0 METs. Total physical activity (MET-min per week) was calculated by summing the three physical activity categories.

Time spent in vigorous intensity activity, moderate intensity activity and walking were calculated by multiplying the typical duration (in minutes) by the frequency (in days) to produce a minutes per week value.

In line with previous research conducted by Maddison et al. (2007) and Nang et al. (2011), energy expenditure from physical activity (PAEE) was calculated. It was assumed that 1 MET was equivalent to 1kcal/kg/hr for all subjects (Maddison et al. 2007). Adopting this approach, the appropriate MET value for each activity category were multiplied by the subject’s body weight (kg) and then divided by 60 minutes to convert this unit to kcal/min. These values were then multiplied by the duration of each activity category and summed to produce a weekly PAEE energy expenditure value in kcals which was then divided by seven to get PAEE in kcal/day.

9.3 DATA ANALYSIS

All analyses were completed using PASW version 18.0. Level of significance was defined as p < 0.05.

Normality was assessed by use of boxplots, histograms, Quantile-Quantile plots and the Shapiro-Wilk or Kolmogorov-Smirnov statistic where appropriate. A number of variables were found to be non normally distributed and thus were transformed to a normal distribution to allow for parametric analyses. As parametric analysis was conducted, in remaining true to the analysis utilised, it was deemed appropriate to report energy expenditure values using the back transformation where necessary. Back transformation was conducted using the exponential or square as appropriate. Thus, where transformations have been used the geometric mean and 95%
confidence intervals for energy expenditure variables are reported. For consistency, where transformations have not been used due to the normal distribution of some variables, mean and 95% confidence intervals have also been reported.

Demographic variables did not exhibit a non normal distribution. Therefore, mean and standard deviations are reported for these variables.

9.3.1 Transformations
For the total sample, logarithm transformations were utilised for the Vigorous Time, Moderate Time and PAEE outputs of the IPAQ-SF while the square root transformation was used for the total IPAQ-SF score as well as the Sitting Time and Walking Time outputs. For the male subsample, logarithm transformations were used for the Sitting Time, Vigorous Time and PAEE outputs of the IPAQ-SF while the total IPAQ-SF score and the Moderate Time output were transformed using the square root transformation. For the female subsample, logarithm transformations were used for the Vigorous Time, Moderate Time and PAEE outputs of the IPAQ-SF. The square root transformation was used for the total IPAQ-SF score and the Walking Time output as well as the SWA output of PAEE. In order to allow assessment of agreement, logarithm transformations were also used on the PAEE outputs of the SWA for both the total sample and the male subsample for Bland and Altman and ICC analyses.

9.3.2 Statistical Analysis
The IPAQ outputs of total physical activity, moderate intensity time, vigorous intensity time, walking time and sitting time were compared to the SWA outputs of TEE and PAEE. This was conducted by use of Pearson’s correlation coefficient. Pearson’s correlation coefficient statistic was used to analyse the strength and direction of the relationship between the IPAQ outputs of total physical activity, vigorous intensity time, moderate intensity time, walking time and sitting time compared to the SWA outputs of TEE and PAEE. The benchmarks for correlations set forth by Cohen, 1988 (Cohen 1988) were used whereby $r = 0.10 – 0.29$ was considered small, $r = 0.30 – 0.49$ was considered medium and $r = 0.50 – 1.0$ was considered strong.
As reported by Deng et al. (2008), a number of variables including gender and age are known to potentially affect the relationship between self report and objective measures of physical activity. For this reason, the strength of the relationship was assessed separately for males and females and partial correlations were used to control for the effects of age.

To examine the level of agreement between the IPAQ PAEE and SWA PAEE outputs, Bland and Altman plots (Bland and Altman 1986, Altman and Bland 1983) were produced. This was conducted for the entire group and also for male and female subjects separately. For each series, the Y axis represented the difference in PAEE between the IPAQ and SWA. The X axis of these plots represents the mean of PAEE IPAQ and PAEE SWA. The limits of agreement (dotted lines) equalling 1.96 standard deviations of the mean difference above and below the mean (solid line) were plotted. The % difference between the two measures were also calculated and presented.

A two-way mixed, single measure, interclass correlation [ICC (3,1)] was used to assess the extent of agreement between the activity monitor and the criterion measures for both step count and energy expenditure. The benchmarks for ICC set forth by Landis and Koch (1977) whereby 0.00 - 0.20, 0.21 – 0.40, 0.41 – 0.60, 0.61 – 0.80 and 0.81 – 1.00 indicate poor, fair, moderate, substantial and almost perfect agreement respectively were used.

9.4 RESULTS
The subjects’ demographic characteristics are shown in Table 9.1.
TABLE 9.1 DESCRIPTIVE CHARACTERISTICS OF STUDY SUBJECTS

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total sample Mean(SD)</th>
<th>Males Mean (SD)</th>
<th>Females Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60.25 (12.71)</td>
<td>58.74(9.02)</td>
<td>61.11(14.66)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.6 (9.2)</td>
<td>171.3 (3.7)</td>
<td>162.3 (9.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.5 (16.4)</td>
<td>85.1 (10.5)</td>
<td>77.8 (18.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.26 (4.96)</td>
<td>29.02 (3.43)</td>
<td>29.40 (5.78)</td>
</tr>
<tr>
<td>Sex (n/%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (63.64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (36.36%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9.4.1 Concurrent Validity of the IPAQ-SF: Overall Physical Activity Level

A correlation of $r = 0.356$ (p = 0.104) was exhibited between the Total IPAQ-SF score and TEE. When age was accounted for this correlation was stronger with a finding of $r = 0.449$ (p = 0.041). The sample was analysed separately for males and females with males demonstrating a stronger correlation between Total IPAQ-SF and TEE than females ($r = 0.523$, p = 0.183 compared to $r = 0.153$, p = 0.601) (Table 9.2).

A correlation of $r = 0.364$ (p = 0.095) was exhibited between the Total IPAQ-SF score and PAEE. Again, when age was accounted for the correlation strengthened, with a finding of $r = 0.384$ (p = 0.085). Similar to the finding of TEE, males showed a stronger correlation between the Total IPAQ-SF score and PAEE than females ($r = 0.544$, p = 0.163 compared to $r = 0.216$, p = 0.459) (Table 9.2).
9.4.2 Concurrent Validity of the IPAQ-SF: Specific Levels of Intensity

9.4.2.1 Sitting Time
The sitting time component of the IPAQ-SF typically negatively correlated with SWA TEE and PAEE values indicating that more an individual sat, the less energy they expended. The strongest correlation between the Sitting Time component of the IPAQ-SF and TEE was for males (r = -0.698, p = 0.054). Similarly, the strongest correlation between the Sitting Time component of the IPAQ-SF and PAEE was for males (r = -0.719, p = 0.044).

9.4.2.2 Walking Time
The strongest correlation between the Walking Time component of the IPAQ-SF and TEE was for males after age was accounted for (r = 0.438, p = 0.325). The strongest correlation between the Walking Time component of the IPAQ-SF and PAEE again was for males after accounting for age (r = 0.528, p = 0.528).

9.4.2.3 Vigorous Time
The strongest correlation between the Vigorous Time component of the IPAQ-SF and TEE was for males when age was accounted for (r = 0.795, p = 0.033). Similarly, the strongest correlation between the Vigorous Time component of the IPAQ-SF and PAEE was also for males after age was accounted for (r = 0.828, p = 0.021).

9.4.2.4 Moderate Time
The strongest correlation between the Moderate Time component of the IPAQ-SF and TEE was for males after accounting for age (r = 0.902, p = 0.005). Similarly, the strongest correlation between the Moderate Time component of the IPAQ-SF and PAEE was also for males after age was accounted for (r = 0.876, p = 0.010). Males consistently showed a stronger correlation than females between all components of the IPAQ-SF and the SWA outputs of TEE and PAEE.

The vigorous time component of the IPAQ-SF consistently showed strongest correlations with for all SWA outputs, and typically strengthened when age was controlled for.
### TABLE 9.2 CORRELATIONS BETWEEN SWA OUTPUTS AND IPAQ-SF OUTPUTS

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total IPAQ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEE</td>
<td>$r = 0.356; \ p = 0.104$</td>
<td>$r = 0.523; \ p = 0.184$</td>
<td>$r = 0.153; \ p = 0.601$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.449; \ p = 0.041$</td>
<td>$r = 0.636; \ p = 0.125$</td>
<td>$r = 0.243; \ p = 0.424$</td>
</tr>
<tr>
<td>PAEE</td>
<td>$r = 0.364; \ p = 0.095$</td>
<td>$r = 0.544; \ p = 0.163$</td>
<td>$r = 0.216; \ p = 0.459$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.384; \ p = 0.085$</td>
<td>$r = 0.701; \ p = 0.079$</td>
<td>$r = 0.229; \ p = 0.452$</td>
</tr>
<tr>
<td><strong>Sitting Time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEE</td>
<td>$r = 0.232; \ p = 0.299$</td>
<td>$r = -0.698; \ p = 0.054$</td>
<td>$r = 0.127; \ p = 0.665$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.030; \ p = 0.896$</td>
<td>$r = 0.634; \ p = 0.127$</td>
<td>$r = 0.294; \ p = 0.330$</td>
</tr>
<tr>
<td>PAEE</td>
<td>$r = -0.133; \ p = 0.554$</td>
<td>$r = -0.719; \ p = 0.044$</td>
<td>$r = -0.046; \ p = 0.876$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.030; \ p = 0.898$</td>
<td>$r = 0.704; \ p = 0.097$</td>
<td>$r = 0.108; \ p = 0.726$</td>
</tr>
<tr>
<td><strong>Walking Time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEE</td>
<td>$r = 0.009; \ p = 0.968$</td>
<td>$r = 0.187; \ p = 0.657$</td>
<td>$r = 0.106; \ p = 0.717$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.052; \ p = 0.821$</td>
<td>$r = 0.438; \ p = 0.325$</td>
<td>$r = 0.139; \ p = 0.650$</td>
</tr>
<tr>
<td>PAEE</td>
<td>$r = 0.103; \ p = 0.649$</td>
<td>$r = 0.220; \ p = 0.601$</td>
<td>$r = 0.059; \ p = 0.841$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.134; \ p = 0.562$</td>
<td>$r = 0.528; \ p = 0.223$</td>
<td>$r = 0.076; \ p = 0.805$</td>
</tr>
<tr>
<td><strong>Vigorous Time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEE</td>
<td>$r = 0.579; \ p = 0.005$</td>
<td>$r = 0.755; \ p = 0.030$</td>
<td>$r = 0.232; \ p = 0.425$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.702; \ p &lt; 0.001$</td>
<td>$r = 0.795; \ p = 0.033$</td>
<td>$r = 0.402; \ p = 0.173$</td>
</tr>
<tr>
<td>PAEE</td>
<td>$r = 0.497; \ p = 0.019$</td>
<td>$r = 0.756; \ p = 0.030$</td>
<td>$r = 0.044; \ p = 0.881$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.505; \ p = 0.020$</td>
<td>$r = 0.828; \ p = 0.021$</td>
<td>$r = 0.051; \ p = 0.869$</td>
</tr>
<tr>
<td><strong>Moderate Time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEE</td>
<td>$r = 0.465; \ p = 0.029$</td>
<td>$r = 0.731; \ p = 0.040$</td>
<td>$r = 0.355; \ p = 0.213$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.463; \ p = 0.034$</td>
<td>$r = 0.902; \ p = 0.005$</td>
<td>$r = 0.298; \ p = 0.323$</td>
</tr>
<tr>
<td>PAEE</td>
<td>$r = 0.376; \ p = 0.085$</td>
<td>$r = 0.674; \ p = 0.067$</td>
<td>$r = 0.326; \ p = 0.256$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.330; \ p = 0.144$</td>
<td>$r = 0.876; \ p = 0.010$</td>
<td>$r = 0.265; \ p = 0.382$</td>
</tr>
</tbody>
</table>
9.4.3 Absolute Agreement
Median PAEE values for SWA and IPAQ-SF for the total sample and male and female subsamples are presented in Table 9.3.

**TABLE 9.3 PAEE VALUES FOR SWA AND IPAQ-SF**

<table>
<thead>
<tr>
<th></th>
<th>SWA PAEE (kcal/week)</th>
<th>IPAQ PAEE (kcal/week)</th>
<th>% Under-/Over-estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>592.28</td>
<td>351.54</td>
<td>40.65% underestimation by IPAQ</td>
</tr>
<tr>
<td>Males</td>
<td>912.69</td>
<td>445.61</td>
<td>51.18% underestimation by IPAQ</td>
</tr>
<tr>
<td>Females</td>
<td>267.89</td>
<td>151.88</td>
<td>43.30% underestimation by IPAQ</td>
</tr>
</tbody>
</table>

The correlation between the SWA PAEE output and the IPAQ PAEE output was $r = 0.407$, $p = 0.060$. When males were assessed separately the correlation was $r = 0.774$, $p = 0.024$ while when females were assessed, the correlation was $r = 0.216$, $p = 0.459$. When age was controlled for, it typically strengthened the correlation between the SWA PAEE and the IPAQ-SF PAEE outputs with correlations of $r = 0.414$, $p = 0.062$ for the total group and $r = 0.763$, $p = 0.046$ and $r = 0.206$, $p = 0.499$ for the male and female subsamples respectively (Table 9.4).

**TABLE 9.4 CORRELATIONS BETWEEN SWA PAEE OUTPUT AND IPAQ PAEE OUTPUT**

<table>
<thead>
<tr>
<th></th>
<th>Pearson’s Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>$r = 0.407; p = 0.060$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.414; p = 0.062$</td>
</tr>
<tr>
<td>Males</td>
<td>$r = 0.774; p = 0.024$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.763; p = 0.046$</td>
</tr>
<tr>
<td>Females</td>
<td>$r = 0.216; p = 0.459$</td>
</tr>
<tr>
<td>Age</td>
<td>$r = 0.206; p = 0.499$</td>
</tr>
</tbody>
</table>
At a group level, using mean scores for normally distributed variables and median scores for non normally distributed variables, compared to SWA, IPAQ-SF tended to underestimate PAEE by 27.64%. When assessing males only, there was a 58.09% underestimation of PAEE by IPAQ-SF, whereas when assessing females only, there was a 43.30% underestimation of PAEE by IPAQ-SF (Table 9.3).

At an individual level, Bland and Altman analysis was utilised. Compared to SWA, there was underestimation of PAEE by IPAQ-SF for 15 subjects (68.18%), while there was overestimation by seven (31.82%) (Fig 9.1). When this is broken down by gender, compared to SWA there was underestimation of PAEE by IPAQ –SF by six males (75%) and overestimation by two males (25%) (Fig 9.2). In females, there was underestimation by IPAQ-SF by ten subjects (66.67%) and overestimation by five (33.33%) (Fig 9.3).

ICC analyses also assessed the extent of agreement between the two measures. For the total sample, ICC = 0.331 (p = 0.154) was found. For the male sample, ICC = 0.374 (p = 0.251) was found and in the female sample, ICC = 0.212 (p = 0.326) was found.

**FIGURE 9.1 BLAND AND ALTMAN PLO FOR PAEE (TOTAL SAMPLE)**
FIGURE 9.2 BLAND AND ALTMAN PLOT FOR PAEE (MALE SAMPLE)

FIGURE 9.3 BLAND AND ALTMAN PLOT FOR PAEE (FEMALE SAMPLE)
9.5 Discussion
To the best of our knowledge this is the only study to date which has examined the concurrent validity of the IPAQ-SF in the RA population. This is despite the frequent use of the IPAQ-SF to measure physical activity and monitor intervention in the RA population (Metsios et al. 2007, Eppeland et al. 2009, Elkan et al. 2009, Metsios et al. 2009). In the present study, the SWA was considered the criterion measure for concurrent validity. Measurements for SWA were performed for the same time period as for the IPAQ-SF and thus it can be assumed that SWA can be considered an appropriate criterion measure. This study found generally small to medium strength correlations between the IPAQ-SF and SWA for the total sample. Females typically demonstrated small strength correlations while males typically demonstrated large strength correlations.

9.5.1 Correlational Analyses
Work conducted recently by van Poppel et al. (2010) suggested that correlations of \( \geq 0.5 \) between accelerometer energy expenditure and total self report score and \( \geq 0.4 \) between accelerometer and moderate and vigorous self report outputs should be the standard for an acceptable self-report physical activity questionnaire.

In this study, use of the total IPAQ-SF score even when accounting for the effect of age in the total sample and female subsample did not manage to achieve the standard of \( \geq 0.5 \) set. The largest correlation achieved was \( r = 0.441 \) (p = 0.041) for when IPAQ-SF was compared to TEE from SWA with age accounted for in the total sample. In the female subsample, the largest correlation was \( r = 0.243 \) (p = 0.424), again for when the total IPAQ-SF score was compared to TEE with age controlled for. Conversely in the male subsample, the total IPAQ-SF score achieved correlations greater than 0.5, both with and without age accounted for. The strongest correlation was found between the total IPAQ-SF score and PAEE after age had been accounted for \( r = 0.701; \ p = 0.079 \).

Use of the IPAQ-SF vigorous time component does achieve the recommended correlation of \( \geq 0.4 \) standard set by van Poppel et al. (2010) for a number of SWA variables. This was found for both of the SWA variables assessed in the male subsample with the strongest correlation of \( r = 0.828 \) (p = 0.021) found for PAEE after age was accounted for. This standard was also reached in the total sample for
both TEE and PAEE ($r = 0.579$ and $r = 0.497$ respectively) but was strengthened for TEE and PAEE when age was accounted for ($r = 0.702$ and $0.505$ respectively). In the female subsample, this standard was only reached for one SWA variable, namely TEE with age accounted for ($r = 0.402; p = 0.173$).

When comparing the IPAQ-SF moderate time component to the SWA variables, again in the male subsample, the IPAQ-SF reached the standard of $\geq 0.4$ for all of the SWA variables, with the largest correlation found TEE with age accounted for ($r = 0.902; p = 0.005$). In the total sample, TEE with and without age accounted for reached this standard ($r = 0.465; p = 0.029$ and $r = 0.463; p = 0.034$ respectively). This standard was not reached with the IPAQ-SF moderate time component was compared to the SWA variables in the female subsample.

Prince et al. (2008) conducted a systematic review which compared objective versus self-report measures for assessing physical activity in 187 studies and found that there was generally a low to moderate correlation between both outcome measures with a mean correlation co-efficient of 0.37. In the RA population, Semanik et al. (2011), found correlations ranging from 0.00 to 0.51 between the Actigraph accelerometer and the Yale Physical Activity Survey. Specifically making reference to the IPAQ-SF, Lee et al. (2011) conducted a systematic review examining the validity of the IPAQ-SF. This review reported a median correlation of 0.29 after examination of 23 studies. Craig et al. (2003) found correlations between 0.02 and 0.47 between IPAQ-SF “last 7 day recall” and the CSA accelerometer, assessed in six sites worldwide. The results of our study compare similarly, showing correlations of $r = 0.356 (p = 0.104)$ when compared to TEE from SWA and $r = 0.364 (p = 0.095)$ when compared with PAEE from SWA.

Prince et al. (2008) found higher mean correlations in male only studies (0.47) compared to female only studies (0.36). Similar results were also found in the results of the present study with correlations between the total IPAQ-SF score and TEE from SWA of $r = 0.523 (p = 0.184)$ for males and $r = 0.153 (p = 0.601)$ for females and correlations between the total IPAQ-SF score and PAEE from SWA of $r = 0.544 (p = 0.163)$ for males and $r = 0.216 (p = 0.459)$ for females.
Lee et al. (2011) also found that some studies reported stronger correlations when the IPAQ-SF was divided into its specific components. This finding was mirrored in the present study with vigorous time and moderate time components of the IPAQ-SF typically exhibiting stronger correlations to both TEE and PAEE SWA outputs than the total IPAQ-SF score.

In terms of utilising IPAQ-SF in RA population as, it is important to note that a large discrepancy exists between the strength of the correlations found in the male subsample and the female subsample. Thus, based on the guidelines set down by Cohen (1988) and van Poppel et al. (2010), we would recommend the use of the IPAQ-SF in terms of its total score as its various individual outputs are comparables of the SWA outputs in the male RA population. We would not recommend the use of the IPAQ-SF in the female RA population however.

9.5.2 Absolute agreement

Lee et al. (2011) reported that very few studies have evaluated the accuracy of the IPAQ-SF (i.e. the concordance of absolute values between the measure obtained by an objective measure and that by the IPAQ-SF) and recommended that further validation studies are needed using this research technique. Correlation analysis is limited as it is only able to measure the strength of the relationship between two variables and cannot assess the level of agreement between them (Bland and Altman 1986). The Bland and Altman and ICC methods provide methods by which the level of agreement between SWA PAEE and IPAQ-SF PAEE can be assessed. Furthermore, Lee et al. (2011) noted that none of the studies included in their review which assessed the accuracy of the IPAQ-SF computed the % over/under estimations of physical activity or used the absolute difference as an indicator of validity. The present study sought to rectify this position.

This study found that the IPAQ-SF underestimated PAEE by 40.65% when compared to SWA for the total sample. The underestimation was also found in the male individuals (51.18% underestimation) and in the female subsample which demonstrated an underestimation by the IPAQ-SF of 43.30 %. Although the individual studies included in the systematic review did not report this over/under estimation, Lee et al. (2011) calculated these and found a range of between a 28% underestimation to 173% overestimation by IPAQ-SF in six studies, with a mean of
106% overestimation reported. The majority of studies (five out of six) reported an overestimation. Prince et al. (2008) also reported that self-report tools tended to overestimate when compared to objective measures (60% overestimation) and when specifically limited to accelerometers showed a mean 44% overestimation. In particular, Prince et al. (2008) reported that females tended to overestimate to a larger degree than male subjects (138% overestimation for females compared to 44% overestimation for males). These results differ from our studies in which IPAQ-SF underestimated physical activity.

Only fair agreement (ICC = 0.331, 0.374, 0.212) for total, male and female samples respectively was found between the SWA measure of PAEE and the IPAQ-SF measure of PAEE.

Thus, based on the Bland and Altman and the ICC analyses would indicate that the IPAQ-SF would not accurate as a measure of PAEE in the RA population.

**9.5.3 Potential explanations**

**9.5.3.1 Correlational analyses**

One explanation which may in part explain the small strength correlations noted predominantly between the IPAQ-SF and SWA outputs may be related to the questions posed in the questionnaire. Despite the fact that the purpose of the IPAQ-SF is to provide estimates of physical activity ([www.ipaq.ki.se](http://www.ipaq.ki.se)), it does not have the ability to account for activities of less than ten minutes duration, whereas SWA captures all forms of physical movements. However, this does not explain why large strength correlations were typically found in the male subsample.

Floor or ceiling effects are considered to be present if >15% of people have the lowest or highest possible score (McHorney and Tarlov 1995). In our study, 18.18% of the total sample and 21.43% of the female subsample reported the lowest score (0) on the IPAQ-SF total score and McHorney and Tarlov (1995) report that this may limit the reliability and responsiveness of the scale.

A further limitation with the use of the IPAQ-SF is that a single estimate of the energy cost of a specific activity, taken from a published compendium (Ainsworth et al. 2000) is applied to all individuals. This does not take inter-individual variation in
energy expenditure due to variations in mechanical efficiency (Terwee et al. 2010) and of particular importance in the RA population, does not take into account variations in metabolism due to the concurrent presence of rheumatoid cachexia (Roubenoff et al. 2002, Metsios et al. 2007) and the resultant differences in resting energy expenditure (Metsios et al. 2008a, Roubenoff et al. 1994) indicative of this group. However, the published estimates of energy costs are the only such data currently available.

The strongest correlations were noted between the SWA TEE and PAEE and the vigorous and moderate time of the IPAQ-SF. This is likely to be because SWA captures energy expenditure, which takes into account intensity. The opposite of this is found in the study conducted by Deng and colleagues (2008), who found poor correlations with the vigorous and moderate time components due to use of pedometers as the criterion measures, which do not capture intensity.

9.5.3.2 Absolute Agreement
The discrepancies noted between the absolute agreement of the IPAQ-SF and SWA may also be explained to some degree. Firstly the IPAQ is not specifically designed to measure PAEE, rather MET values. Similar to the work of Maddison et al. (2007) PAEE was estimated from MET mins, which may have contributed to the underestimation of energy expenditure. Furthermore, as has been previously outlined, the allocated MET values from the IPAQ-SF scoring protocol may not accurately reflect the intensity of all activities for all people. This is further compounded in the RA population, where the metabolic abnormalities exhibited by the population may further contribute to the discrepancy.

9.6 Conclusion
The correlations determined between varying outputs of the IPAQ-SF and SWA show only small-medium strength correlations for the total sample. This can be broken down however into male and female subsamples in which the female subsamples typically show small strength correlations while the male subsamples show large strength correlations.
As an absolute measure, the results of this study also demonstrate that the IPAQ-SF tends to underestimate PAEE in this population when compared to SWA and shows limited agreement.

As a result, the evidence provided by this study suggests that the IPAQ-SF has limited use for estimating physical activity in the RA population either as an accurate and absolute measure of physical activity. Furthermore, it is suggested that it not be used as a relative measure of physical activity in the female population. However considering the standards recommended by Cohen (1988) and van Poppel et al. (2010), its use is recommended in the male RA population as a relative, but not absolute measure of physical activity.

Comparing the results of this study involving individuals with RA with other studies assessing the IPAQ-SF have found similar findings, indicating that the IPAQ-SF has a similar validity in the RA population as it has in other populations.
SECTION 3

This section encompasses a single chapter of this thesis (Chapter 10), which is a piece of work which has recently been published.

This chapter is a qualitative piece which will outline an examination of the subjects’ perspective of the use of technology in the monitoring of physical activity, which may highlight its prospective use in this population.
CHAPTER 10 USERS' EXPERIENCE OF PHYSICAL ACTIVITY MONITORING TECHNOLOGY IN RHEUMATOID ARTHRITIS

(Tierney M. Fraser A. and Kennedy N. “Users' Experience of Physical Activity Monitoring Technology in Rheumatoid Arthritis”. Musculoskeletal Care, 2012 (Epub ahead of print DOI: 10.1002/msc.1034))
10.1 INTRODUCTION

Dramatic increases in the numbers of chronically ill patients in conjunction with declining provider numbers and significant cost pressures mean that fundamental change is required in methods of health care provision (Paré et al. 2007). Monitoring health outcomes in the home using technological means is one such alternative. With regard to physical activity assessment, monitoring in the home setting has even greater benefits, providing a realistic image of habitual physical activity levels. However, there are few studies available that assess the beliefs of the technology users regarding the benefits of using technology in the home setting to monitor health outcomes.

As outlined by Norman (2002), there is a large degree of variance in the understanding of the device between the designer and the user. The designers are experts on the device; however the users are the experts of the task which the device is aiming to perform. The technology acceptance model (TAM) (Davis et al. 1989) dictates a potential users acceptance or rejection of computer based technology. TAM, which has been widely used in healthcare settings (Holden and Karsh 2010), involves two primary predictors – perceived ease of use and perceived usefulness. Users are able to provide valuable insight into the user-acceptance of these technological devices and determine whether they will be accepted and incorporated into general use. Understanding what makes a technology easy to use and user-friendly helps improve the design (Lehoux 2004). Involvement of users in the assessment of medical device technology has been deemed “essential” by Shah and Robinson (2007) to improve their ease of use for the end user.

Jimison et al. (2008) reported that the primary barrier to the use of technology was the notion that if the study participants did not perceive there was a benefit to be derived from the use of the technology, they were unlikely to engage with it. Thus, determining the user’s perspective on technology is imperative and will play an important role in the utilisation of the technology on a larger scale.

The aim of the present study was to qualitatively explore the experiences of home monitoring of health with specific regard to physical activity monitors worn over a seven day period in people with RA.
10.2 METHODOLOGY

A qualitative study, using focus groups as the data collection method, was the preferred study design in order to capitalise on the interaction that occurs between research participants during the discussions (Grønkjær et al. 2011, Ho 2011). Focus groups are regarded to be particularly suited to providing in-depth information on a topic and find out peoples’ ideas, experiences, beliefs and emotions on the topic, as well as highlighting differences in opinion, creating further generation of ideas (Krueger and Casey 2000, Rabiee 2004) and are commonly used in health research.

10.2.1 SUBJECTS

Subjects were randomly selected from a larger sample (n=75) of individuals with RA who had taken part in a physical activity monitoring study. At the end of the monitoring period, all 75 participants who completed seven full days of monitoring were provided with an information sheet and offered the opportunity to participate in this qualitative study. Fifty individuals expressed an interest in participating. As no specific characteristics were required to warrant a specific purposive sampling strategy, 20 of the 50 individuals were randomly chosen using a random number generator (www.random.org) to take part in the focus groups. Six of the 20 subsequently reported that they were no longer willing to take part in the study and so a total of 14 subjects took part in one of two focus groups.

All subjects had worn two physical activity monitors (SWA and SHIMMER) for a period of seven days within the previous six months.

10.2.2 PROCEDURES

Each participant provided written informed consent to participate in this study. The focus groups were both hosted in the rheumatology infusion room which is a quiet private room with ample space, located at the Mid Western Regional Hospital, Croom, Limerick. This was a location which was deemed suitable to all the participants. Each focus group lasted between 40 minutes and one hour. The discussions were facilitated by a moderator (MT), accompanied by an assistant who was unrelated to the study, who recorded non-verbal communication and points of note in the discussion. The discussion was audio-taped with the permission of the participants, using a digital recorder.
The focus group began with an introduction from the moderator outlining a brief description of the nature of a focus group, affirming anonymity and explaining each person could contribute as much or little as he or she wished during the discussion. The questioning route, which was developed in order to best meet the aims of the study, is outlined in Table 10.1 and followed in a manner similar to that recommended by Krueger et al. (1998). Probing was used to expand vague expressions where necessary. The focus group concluded with the moderator summarising the discussion, questioning participants as to whether this was a fair representation of the discussion and inquiring if any individual wished to contribute any further points.

Immediately following the focus group, a debriefing session was held between the moderator and assistant to discuss overall impressions and main ideas which were highlighted during the discussion. Summary notes were recorded based on this discussion.
**TABLE 10.1 QUESTIONING ROUTE**

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you feel it was worthwhile to find out about your physical activity levels?</td>
<td></td>
</tr>
<tr>
<td>Have you ever had any other experience of having your health monitored at home?</td>
<td></td>
</tr>
<tr>
<td>Elaborate</td>
<td></td>
</tr>
<tr>
<td>How did you feel about having your health monitored at home rather than in the hospital setting?</td>
<td></td>
</tr>
<tr>
<td>Positives and negatives</td>
<td></td>
</tr>
<tr>
<td>Were there any negative aspects of wearing the SHIMMER/SWA for one week?</td>
<td></td>
</tr>
<tr>
<td>Would you make any changes to the monitors to make them more user friendly?</td>
<td></td>
</tr>
<tr>
<td>Elaborate</td>
<td></td>
</tr>
<tr>
<td>Did you feel you made any changes whilst undertaking the study?</td>
<td></td>
</tr>
<tr>
<td>Daily routine</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
</tr>
<tr>
<td>Did you feel that your focus on your physical activity levels changed whilst you were wearing the SHIMMER/SWA?</td>
<td></td>
</tr>
<tr>
<td>Do you feel that your focus on your physical activity levels have changed after wearing the monitors and finding out about your activity levels?</td>
<td></td>
</tr>
</tbody>
</table>

**10.2.3 DATA ANALYSIS**

Theoretical thematic analysis was conducted using a semantic approach, as outlined by Braun and Clarke (2006). Initially, the audio tapes were transcribed verbatim with subjects names coded to ensure anonymity. Repeated reading of the transcripts was then undertaken to allow for immersion in and familiarisation with the data. Analysis of data was aided by an evaluation of assistant’s observational notes and summary notes completed after the debriefing session as recommended by Rabiee (2004). The next phase in the analysis involved coding. Codes identify features of the data which are reflective of the meaning of a particular statement. Transcripts were examined on a line by line basis to examine each statement, and all statements were grouped into a particular code. Codes were interpreted and analysed with respect to “words”, “frequency”, “intensity of comments”, “specificity of responses” and
“extensiveness” in accordance with the recommendations of Krueger, (1994), Krueger and Casey (2000) and Rabiee (2004). Themes were then developed by sorting the various codes into broader levels. Reviewing and refinement of themes followed to allow for data within themes to link together and all themes to be distinctive from one another. Member checking and completion of an audit trail were conducted in order to validate procedures based on assumptions related to the study participants (member checking) and people external to the study (audit trail) (Creswell and Miller 2000).

10.3 RESULTS
10.3.1 DEMOGRAPHICS
The demographic variables of the participants are presented in Table 10.2 and 10.3. Their age range was 43.91-74.55, with a disease duration ranging from 0.50-26 years. The mean score on the DAS-28 was 3.76, indicating that, on average participants had moderate disease activity. The mean score on the HAQ was 1.145, indicating that, on average; participants had some degree of disability. Those in group 2 were, on average, younger than those in group 1 with lower DAS-28 and HAQ scores and higher self reported disease duration.

TABLE 10.2 DEMOGRAPHIC PROFILE OF GROUPS OF PARTICIPANTS

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female/Male)</td>
<td>8/2</td>
<td>3/1</td>
<td>11/3</td>
</tr>
<tr>
<td>Age (years±SD)</td>
<td>60.09±9.49</td>
<td>52.40±8.47</td>
<td>57.90±9.59</td>
</tr>
<tr>
<td>Disease duration (years±SD)</td>
<td>9.30±7.21</td>
<td>12.13±10.52</td>
<td>10.11±7.96</td>
</tr>
<tr>
<td>Disease activity (DAS-28 score±SD)</td>
<td>4.28±0.83</td>
<td>2.47±0.50</td>
<td>3.76±1.12</td>
</tr>
<tr>
<td>Health assessment (HAQ-DI score±SD)</td>
<td>1.45±0.58</td>
<td>0.39±0.38</td>
<td>1.15±0.72</td>
</tr>
<tr>
<td>Participant</td>
<td>Gender</td>
<td>Age (years)</td>
<td>Disease duration (years)</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>1(a)</td>
<td>Female</td>
<td>51.21</td>
<td>2</td>
</tr>
<tr>
<td>1(b)</td>
<td>Female</td>
<td>64.67</td>
<td>12</td>
</tr>
<tr>
<td>1(c)</td>
<td>Female</td>
<td>60.52</td>
<td>11</td>
</tr>
<tr>
<td>1(d)</td>
<td>Female</td>
<td>60.36</td>
<td>15</td>
</tr>
<tr>
<td>1(e)</td>
<td>Female</td>
<td>44.13</td>
<td>15</td>
</tr>
<tr>
<td>1(f)</td>
<td>Male</td>
<td>70.27</td>
<td>11</td>
</tr>
<tr>
<td>1(g)</td>
<td>Female</td>
<td>74.28</td>
<td>22</td>
</tr>
<tr>
<td>1(h)</td>
<td>Male</td>
<td>47.90</td>
<td>2</td>
</tr>
<tr>
<td>1(i)</td>
<td>Female</td>
<td>63.63</td>
<td>2</td>
</tr>
<tr>
<td>1(j)</td>
<td>Female</td>
<td>60.41</td>
<td>1</td>
</tr>
<tr>
<td>2(a)</td>
<td>Female</td>
<td>55.90</td>
<td>26</td>
</tr>
<tr>
<td>2(b)</td>
<td>Male</td>
<td>43.70</td>
<td>0.50</td>
</tr>
<tr>
<td>2(c)</td>
<td>Female</td>
<td>62.03</td>
<td>12</td>
</tr>
<tr>
<td>2(d)</td>
<td>Female</td>
<td>46.95</td>
<td>10</td>
</tr>
</tbody>
</table>

### 10.3.2 THEMATIC RESULTS

Discussions followed similar themes across both focus groups. Through the process of thematic analysis, three key themes (experience of having health monitored in the home, experiences of specific technology and perceptions and experiences of physical activity and exercise) predominated. The quotes below are identified by group (Group 1 = 1, Group 2 = 2) and then by participant number (e.g. a, b).
10.3.2.1 Experience of having health monitored in the home

Overwhelmingly, participants felt that having their health monitored in the home was a positive thing and were “delighted” with it. Ten participants expressed positivity with health monitoring in the home.

People were conscious that health service resources were limited by the current economic situation and that home monitoring could be a viable cost effective alternative:

“The advantages would be huge you know from the cost point of view if people could be kept out of hospital” (1h)

People were also mindful that the home situation would give a more realistic picture, and thus be more representative of the health of a person:

“When you go to hospital you’re kinda hyped a little bit and everything is up a bit whereas if you were monitored at home, everything is normal” (2b)

People were also aware of the hazards associated with attendance at hospitals, particularly for those on immunosuppressant therapy which would represent a large proportion of people with RA:

“The way things are going in the hospital at the moment with all these bugs and the whole lot, I’d prefer to be monitored at home” (2b)

People also liked the fact that they were more in control of their condition and its management:

“And people involved more in their own treatment rather than havin’ it done to them” (1h)

However, people expressed that they would not be happy to leave all aspects of their health to be monitored by themselves and in the home and saw the benefit and necessity of attendance at the hospital for certain monitoring:

“Would like to attend the rheumatologist still” (1j)
10.3.2.2 Experiences of specific technology

Some individuals also reported that the wearing of the monitors in the home made them more conscious about increasing their activity levels and thus perhaps indicating that an unrealistic finding was reported:

“I must admit, I did. I was conscious of the fact that I said I’d walked, I’d better walk as much as possible” (2c)

The majority of people did not find the monitors to be obtrusive or feel that they were an imposition in their lives, with eleven participants reporting aspects outlining this.

It was also felt that home monitoring in this way allowed people to continue to live life normally and unaffected which was considered to be a positive aspect and something which would not typically occur if the monitoring was conducted in the clinical setting

“I just done my normal kind of routine” (2b)

Participants were generally positive about wearing the monitors, although the preferred monitor was the arm device (SWA) as it was felt to be more comfortable to wear. Only one participant reported a problem with SWA use. Problems with the SHIMMER related mainly to the way it fixed on the thigh with ten participants reporting problems with securing it. Participants provided useful feedback on ways to improve the design of both monitors, particularly the SHIMMER, to make them more user friendly and, thus, increase the potential wear and the accuracy of the result. The feature that most people commented on was the way in which the SHIMMER was secured:

“If you have the actual monitor secured in something so that it’s actually not going to move, secured within some kind of compartment on the strap. A pouch or something” (2c)

Some people also felt that the location of the SHIMMER could be altered, with the ankle being the preferred location:

“Down low on the ankle I think would be easier to work with” (1d)
10.3.2.3 Perceptions and experiences of physical activity and exercise

Participants had an overwhelmingly positive response to learning about their physical activity levels, with increased awareness expressed most frequently:

“I must admit it’s made me conscious” (2c)

People expressed that learning more about their own physical activity levels had motivated them to keep working to at increasing them:

“I’m very happy with them results cause I’m forever thinking I should do more….. I’d have every excuse….. not to walk” (2a)

Others found that they were happy with the results and felt that they showed they were doing well:

“I know that I’m on the right track” (2a)

Conversely, others felt that, although they would have liked to increase their activity levels, this might not have been possible:

“Sure we’d love to be able to do more, but we mightn’t be able to do it” (1c)

Participants seemed to have a good understanding of the fact that physical activity and exercise was good for them and important for them to do especially in light of their RA

“Is definitely (important), I think for later on in years more than anything else” (2b)

However, despite their knowledge of exercise, participants seemed to have very little understanding of the need for pacing of activities with a disease such as RA

“And you pay for it the next day, you mightn’t be able to do nothing for two or three days. And you’re kicking yourself then for doin’ too much, you should have halved it” (1h)
10.4 Discussion
The present study explored the experiences of people with RA who used technology to monitor their levels of physical activity. Overall, participants reported a positive experience of using the technologies, but had some suggestions to improve the devices. The study offers an interesting perspective on technology to measure physical activity by exploring the users’ perspective on and experience of this technology. Most other physical activity studies using a qualitative approach have evaluated individuals’ perceptions about and experiences of physical activity rather than physical activity monitoring and the wearing of monitors in the home setting.

Users’ experiences of physical activity monitoring have been assessed by a small number of studies, but none have been conducted in rheumatology populations. Ahtinen et al. (2008) assessed users perspectives of using heart rate monitors to motivate, set goals and learn regarding training effects. Partridge et al. (2011) used qualitative analysis to assess high school students perspectives on use of heart rate monitors in grade setting, understanding training and fitness levels, and their use in a physical education class. Heesch et al. (2005) assessed women’s qualitative perspectives of use of a pedometer intervention to increase physical activity levels. The latter study did offer the viewpoints of the users with regard to the wearing of the monitor, its usefulness and complaints associated with it. However, as the monitor was part of an interventional programme, the way in which the monitors were used by the participants (in terms of wear time, feedback received) means that the results of this study have to be interpreted slightly differently to those of the present, study which aimed to monitor physical activity levels.

10.4.1 Experiences of Having Health Monitored in the Home
A systematic review of telehealth (defined as telecommunication technologies to support healthcare and education across some distance) found that users are generally satisfied with telemedical care, reporting benefits such as easier access to specialists, reduced travel, financial savings and increased personalised care (Whitten and Love 2005). The subjects in the present study also made reference to the potential cost savings which could be made from monitoring in the home setting.

The main concern noted by the telehealth systematic review (Whitten and Love 2005) was the potential loss of relationship with healthcare providers and the need to
see the specialist in person from time to time. These issues were also highlighted by participants in the present study indicating that they need to be addressed in the use of telehealth.

Empowerment and independence with regard to the self management of the condition were factors which were raised in our focus groups. Individuals felt that home monitoring enabled this and this finding was also replicated in asthma and stroke populations who undertook peak flow and blood pressure measurements respectively in the home setting (Pinnock et al. 2007, Ovaisi et al. 2011).

The reluctance to attend hospital sites because of the increased risk of infection is an issue likely to be related solely to populations who are on immunosuppressant therapies. However, this finding does raise a further important benefit of home monitoring, unique to this specific population group.

Another aspect mentioned as an experience of home health monitoring by participants of the present study relates to the participants’ impression of a more realistic and representative picture achieved by home monitoring. This feature has not been mentioned as a benefit of home monitoring in this area and, thus, one could ask why this aspect was raised in the RA population. One potential reason may be that the RA population has been shown to have higher levels of anxiety than the general population (VanDyke et al. 2004, Isik et al. 2007), which may indicate that they have higher levels of anxiety when dealing with health professionals. However this has not been assessed to date as it has not been determined if the RA population has higher anxiety levels than other patient populations.

10.4.2 Experiences of specific technology
Users’ perspectives of specifically having their physical activity levels monitored were also explored. As previously mentioned, assessment of users’ experiences of physical activity monitoring is not routinely conducted and, thus, there is little with which to compare our findings.

Habitual physical activity was the construct under investigation. The majority of subjects appeared to understand the rationale of habitual physical activity monitoring and did not modify their physical activity levels indicating that information provided prior to monitoring was sufficient in most cases. However, a minority of individuals
appear to have been affected by the Hawthorne effect and reacted by modifying the
behaviour being measured. As outlined by TAM (Davis et al. 1989), the perceived
ease of use and perceived usefulness are important in determining whether a
technology will be accepted or rejected by a population. Thus, it was necessary to
assess these factors for both of the monitoring tools as this information could prove
useful in the rollout of larger scale projects which aim to improve user-friendliness,
acceptance and adherence.

The literature surrounding home telehealth technology consistently recommends that
systems should be designed to minimise their obtrusiveness to end users (Hensel et
al. 2006) and thus, be perceived as easily used. The results of our focus groups
indicate that the physical activity monitors which were used were perceived as
unobtrusive with regard to the “routine dimension” of obtrusiveness (Hensel et al.
2006). There appeared to be no interference with daily activities and no acquisition
of new rituals was necessary as a result of the wearing of the monitors. This is
particularly encouraging to discover, as when a “change in routine” is demanded by a
new intervention, adherence is much less likely. This is primarily seen in drug
treatment (Schwartz 2005, Gard 2010, Tordoff et al. 2010); however there are also
reports in the rehabilitation setting (Clay and Hopps 2003, Hughes et al. 2006,
Broonen et al. 2011).

The “physical dimension” of the user perception of obtrusiveness (Hensel et al.
2006) was the aspect which SHIMMER seemed to be lacking most frequently,
affecting participants’ perception of ease of use. Both discomfort and obstruction
aspects were mentioned as problematic by participants. The SHIMMER is currently
primarily in the research environment, so there is the potential for more design
changes to occur.

Conversely, the SWA did not seem to invite the same level of obtrusiveness with
most individuals reporting satisfaction with this tool, and only minimal reports of
dissatisfaction, which were related to the “physical dimension”.

As highlighted by Shah and Robinson (2007), the involvement of users in the
development and assessment of medical device technologies is associated with
significant benefits such as improvements in device design and user interfaces as
well as improvements in the functionality, usability and quality of such devices. The novel and creative changes which designers could utilise to improve users’ ease of use relate, naturally, to the issue with which participants reported the largest degree of inconvenience – in this case, the securing of the SHIMMER to the leg.

Changes were also suggested with regard to the location of the SHIMMER and, although was not mentioned as a problem, it was an area users wished to apply change. This could indicate that the location may indeed have proved problematic and may have been related to the “physical dimension” of obtrusiveness or perhaps to embarrassment or stigma which are both aspects of the “self-concept dimension” of obtrusiveness (Hensel et al. 2006). Most participants wanted the monitor to be located lower down on the lower limb, typically at the ankle. The ankle is not a common site at which to place a monitor for physical activity assessment; however the Stepwatch-3 activity monitor is an ankle-worn pedometer, and the ActiGraph and Actical have also been utilised at the ankle. Thus, there is scope to utilise this, perhaps particularly for the RA population.

10.4.3 EXPERIENCES OF PHYSICAL ACTIVITY AND EXERCISE
The Technology Acceptance Model (Davis et al. 1989) indicates that perceived usefulness is also a major predictor of use of a technological innovation. Previous research involving technological innovation in healthcare has often reported that monitoring in the home by new technology methods has benefits which often cannot be achieved by more traditional means. Improvements in self-management (Peel et al. 2004, Seto et al. 2010), empowerment and independence (Pinnock et al. 2007, Ovaisi et al. 2011), motivation of lifestyle change (Peel et al. 2004, Ure et al. 2009, Seto et al. 2010) and increased reassurance (Peel et al. 2004) were reported by users which utilised home monitoring of varying aspects of health.

The subjects in our focus groups also found that learning about their physical activity levels after the period of monitoring was useful and had beneficial effects. Many reported that learning about their physical activity levels served as a motivation to continue to work to improve physical activity levels, and also served to negate “excuse making”. Other users reported the reassurance of being provided with details of their levels of physical activity, providing assurance that they were progressing well.
As many subjects became more conscious and motivated to increase physical activity levels as a result of monitoring, it was deemed necessary to gain an understanding of the users’ knowledge of the beneficial effects of physical activity. It was found that there was mainly good awareness of the importance of physical activity, both for arthritis symptoms and health quality overall among this population group.

10.5 CONCLUSION

Individuals with RA appear to be generally positive about having their health monitored in the home setting and expressed many similar experiences as other populations using other forms of monitoring of health in the home setting.

Our focus groups also highlighted the understanding of the benefits of physical activity and exercise which is endemic of this population group. However, it has also been highlighted that this group may be lacking in some aspects of self management in relation to activity, in particular the ability to pace activities.

Overall, these focus groups were the first to highlight the perceptions of individuals with RA with regard to monitoring of health in the home, particularly in connection with physical activity monitoring. This has implications for those planning interventions for this population group that involve home monitoring. Interesting findings have also been highlighted with regard to this population group’s perceptions and understanding of physical activity and exercise.
CHAPTER 11 GENERAL DISCUSSION
11.1 Introduction

In the preceding chapters, a number of studies relating to physical activity in the rheumatoid arthritis population have been presented.

Validation work was undertaken to determine a measurement tool which could accurately represent a physical activity construct. On the basis of the findings of this study, the SWA energy expenditure output was utilised for the remaining studies.

Studies reporting energy expenditure levels of the RA population, comparison with controls and the correlates of energy expenditure are presented. The relationship between inflammatory markers known to be related to cardiovascular disease and energy expenditure are also presented.

Two additional studies were also undertaken relating to users preferences for physical activity monitoring. Subjective tools are perceived to be preferable and better accepted by subjects due to their low participant burden (Dishman et al. 2001, Prince et al. 2008). Thus, a validation study was conducted for a commonly utilised subjective physical activity measurement tool. Furthermore, the users’ experiences of physical activity monitoring were also assessed qualitatively as part of this thesis.

While the results of each chapter have been discussed individually, the aim of this chapter is to gather together all the findings and explore the overall conclusions from this PhD work. Limitations of this work will be explored and suggestions for future work stemming from this thesis will also be made.

11.2 Discussion of Results

Chapter 2, 3 and 4 reviewed the current literature in the area of physical activity and inflammatory related cardiovascular disease in the rheumatoid arthritis population. Chapter 2 is a discussion piece which aims to inform regarding background information on the rheumatoid arthritis population and physical activity, its constructs and measurement issues. Chapter 3 is a published systematic review paper which seeks to explore the current published evidence to assess the levels of physical activity in the RA population and how the levels compare to control populations. This systematic review, for the first time, collates the evidence conducted to date on
physical activity in the RA population. The conclusions drawn from this chapter indicate that physical activity levels among the RA population may be lowered when compared to healthy controls but methodological considerations prohibit conclusive defining of physical activity levels of this population group, and thereby definitely stating that the physical activity levels of this population are decreased. The methodological concerns related to the use of unvalidated and often subjective measurement tools, use of measurement outputs which do not lend themselves to modulation to allow for comparison with other studies and use of control populations which may not be representative of peers.

The findings reported in Chapter 2 and 3 lead to the development of the studies reported on in Chapter 5 and 7. As physical activity methodology was found to be a concern in Chapter 3, a sound protocol was developed for the measurement of physical activity and was outlined in Chapter 6.

As described in Chapter 3, the use of unvalidated physical activity measurement tools was found to be a problem in this research area, a validation study (Chapter 5) was undertaken to allow for a validated, objective tool to be used to strengthen the results reported in Chapter 7, 8 and 9. As outlined in Chapter 2, the definition of physical activity (Caspersen et al. 1985) contains both the terms “energy expenditure” and “movement”. Thus, as SWA records both the constructs of energy expenditure and steps (movement), this was an obvious choice to examine validity in. Chapter 5, reports that, despite finding it has a tendency to overestimate energy expenditure, the findings, in terms of ICC and correlational analyses, indicate that SWA is a suitable and valid tool with which to represent physical activity in the form of energy expenditure in the RA population. This finding resulted in the use of the SWA energy expenditure output for the remaining studies of this thesis. The results of this study found that the step count output of the tool could not provide valid results for this population and thus, should not be used.

Chapter 6 outlines the protocol for use of SWA which was followed for the studies in Chapter 7, 8 and 9. The physical activity methodology was decided upon based on the findings of previous literature in the area, details of which has been defined in Chapter 2 and 3. In line with recommendations made in Chapter 3, the control
population was drawn from a hospital based population. Data reduction of the SWA output was conducted based on limited information in the area in the general and RA populations, however, the studies conducted by (Scheers et al. 2012a, Scheers et al. 2012b, Almeida et al. 2011). Details outlining how decisions were made regarding valid day, imputation of offbody estimates and REE values are outlined.

Chapter 7 seeks to add to the literature on the topics which have been outlined in Chapter 3, and also seeks to improve on the methodological limitations which were also found by this systematic review. The findings of this study appear to mirror the limited range of literature in terms of TEE buts adds to the literature in a novel way by providing estimates of REE, PAEE and TEE objectively in the RA population without using the more expensive and invasive DLW method. It also finds that PAEE may in fact be lower than previously reported. This chapter also adds to the literature by utilising a drawing the control population from a non-disabled hospital outpatient clinic group, and found that differences appear to exist for the female subsample for PAEE. This chapter also highlights the importance of reporting PAEE rather than TEE in the RA population, mainly in light of the metabolic differences in this group, which have been outlined in Chapter 2.

Among its objectives, Chapter 7 also aims to fill a gap in the literature in relation to the correlates of physical activity in the RA population. As highlighted in Chapter 2, physical activity is a modifiable construct and thus if an understanding can be gained of the specific factors which correlate with physical activity, these can be used through interventional strategies to increase physical activity levels. Despite psychosocial correlates being frequently reported upon in the RA population, demographic and health related factors have been much less well investigated. The findings of this chapter indicate that the targeting of female and unemployed populations seem to represent the groups with greatest potential for improving energy expenditure levels in the RA population.

Chapter 4 provides an outlines of potential explanatory reasons for the increased cardiovascular disease risk in the RA population. As evidenced by the latest research, inflammation is perceived as the key causative factor and thus the literature was further examined to provide an explanation, at least in part, for this link, with regard
paid to the role of specific inflammatory markers. The impact which physical activity plays upon inflammatory markers is examined with a large gap in the literature noted in the RA population, where there is a paucity of studies conducted with only a limited range of markers assessed. Thus, Chapter 8 was developed with the aim of filling this gap in the literature.

In Chapter 8, the relationship between a large range of inflammatory markers known to have an impact upon cardiovascular disease in other populations and energy expenditure was examined. Many of the inflammatory markers which were assessed by this study have not previously been examined in this manner in the RA population. This study unearths some novel and interesting relationships between energy expenditure and inflammatory markers with significant relationships noted between energy expenditure and CRP, ESR, Fibrinogen, SAA and WBC. As this study shows that relationships exist between energy expenditure and inflammatory markers, it may be the case that relationships exist between energy expenditure and inflammation related cardiovascular disease in this population. This study has laid down groundwork which justifies the setting up of further studies if this is the case, and thus, may highlight a means by which to target cardiovascular disease risk in the high risk population. Furthermore, interesting findings have been noted in relation to the point in the inflammatory cascade which the inflammatory markers which are related to energy expenditure have their impact at. Significant relationships were noted for CRP, ESR, Fibrinogen, SAA and WBC (all which have impact later in inflammatory process), while no significant relationships were noted between IL6, IL8, IL10 or TNF-α (which are involved in the initial phases of the inflammatory cascade).

The successful utilisation of any technology is dependent on the users’ perspective and beliefs of the benefits of that technology. If the technology is not utilised correctly (if enough valid wear time is not recorded for example), the accuracy of the results produced may be compromised. There has been an extreme lack of research conducted into home monitoring of health using technology, and none within the RA population. Thus, the study outlined in Chapter 10, adds significantly to the research in this area. The findings of this study were overwhelmingly positive with regard to home monitoring of health and the use of SWA as a physical activity monitoring.
tool. The findings of this study would inspire confidence in the future use of SWA in further studies using this population. However, despite the positivity surrounding SWA, the cost of the tool (€800 + VAT) and the length of time taken to get results may limit its feasibility in longer term studies. Thus, the aim of the study outlined in Chapter 9 was to determine if it would be possible to utilise a subjective physical activity questionnaire to gain a similar output. However, it was found that the IPAQ-SF has only very limited use as an estimate of physical activity in the RA population, either as a relative or absolute measure. Thus, until a subjective tool can demonstrate acceptable validity, the results of this thesis would recommend the continued use of the SWA energy expenditure output as a measure of physical activity in the RA population based on its validity (Chapter 5) and the satisfaction expressed by the users (Chapter 10).

11.3 STRENGTHS OF THESIS

This thesis has many strengths, both in terms of its methodology and the novelty of the topics investigated. It is embedded in previous research and aims to fill gaps in the research noted in the literature reviews conducted and reported on in Chapter 3 and 4 and also aims to utilise best practice protocols in the area.

An objective physical activity monitoring tool was validated for use in free living activity in the RA population (Chapter 5). This is the first instance where an objective physical activity monitor which is suitable for use by a broad spectrum of investigators and clinicians has been validated for this population. The availability of this information adds confidence to the accuracy of the results reported in this thesis, and also provides other researchers with a valid tool with which to work. This validated objective physical activity monitor was utilised for all further physical activity measurements in this thesis.

The control population used for the study outlined in Chapter 7 was chosen based on the findings of the systematic review which indicated that healthy controls and other rheumatic disease control populations were not representative of peers of the RA population. For this reason, an outpatient clinic control population free of physical disabilities was chosen to be used. Furthermore, this study is among the first to
provide details of each of the components of TEE in the RA population. A validated equation which estimates REE in the RA population was utilised to account for the metabolic differences in this population group compared to the general population. The REE equation used for the control population was chosen based that which was deemed most accurate in a systematic review (Frankenfield et al. 2005).

The potential correlates assessed in Chapter 7 were chosen based on previous literature which showed relationships in the normative and other clinical populations but which had not been assessed previously in the RA population. In this manner, this study adds to and fills an identified gap in the literature.

Chapter 4 identified that while a wide range of inflammatory markers have been shown to have associations with physical activity in the normative and other clinical populations, only a limited few have been assessed in the RA population. The aim of Chapter 9 was to fill a gap in the literature, by assessing a wider range of inflammatory markers, chosen based on previous research which indicated their significance in other populations.

A gap in the literature was noted in terms of analysis conducted into individuals’ experiences of using technology in for health monitoring outside the hospital setting. Chapter 10 sought to fill this gap, by assessing this in the RA sample who had used technology to monitor physical activity in the home. The findings of this study will have implications for the successful future use of physical activity monitors in this population.

Subjective physical activity tools have been frequently used in the RA population likely due to their easy and cost efficiency. However, validation work has not been conducted to determine their accuracy. IPAQ-SF has been commonly utilised in the RA population and thus, the study outlined in Chapter 9 sought to assess if this tool could provide an alternative to objective monitoring in the RA population.
11.4 Limitations of Thesis

There are a number of limitations within which the results of this thesis must be considered.

Initially, with regard to the study which assessed the validity of the SWA (Chapter 5), there are a number of potential limitations. Firstly the sample size (n=14) is considered small for a validation study and thus the generalisation of the results may be limited. Furthermore, there was a greater number of males (n=8) than female (n=6). This is in direct contrast to the gender makeup of the typical RA population which is predominantly female. This may impact the generalisation of the findings of this study.

The data reduction techniques utilised for SWA for the seven day monitoring period can also be considered a limitation. Imputation of sleep data rather than a 24hour protocol as is recommended by the manufacturers was used. This may lead to concerns as to the accuracy of the inputted data and also if the off body time which was inputted using sleep data was in fact related to sleep time.

With regard to the blood samples which were recorded, it would have been preferable to have obtained all samples in a fasting manner and at the same time of the day due to the diurnal variation which is known to impact many of this markers, often due to the impact of food. Furthermore, it is know that an acute phase response to exercise can result in an increase in levels of some of the inflammatory markers assessed however it was unable to control for this influence in this study. This response however, appears to be proportional to the amount and intensity of exercise undertaken, with prolonged intense exercise unlikely within this population group.

The sample size of 59 individuals can be considered a limitation, particularly with regard to the regresional analysis conducted as part of the studies included in Chapter 7 and 8. However, the adjusted $r^2$ value as recommended by Tabachnick and Fidell (2007) was utilised to account for this and minimise the impact of this limitation.

Due to the cross sectional nature of the design of the studies outlined in this thesis, a cause and effect relationship cannot be inferred.
11.5 Implications for Practice

This thesis has many implications for those involved and interested in measurement of physical activity, assessment of levels of physical activity and inflammation related cardiovascular disease risk in the RA population.

1. The findings of this study provide the first validated objective physical activity monitoring tool suitable for use in the RA population. Thus, with use of SWA energy expenditure output, both researchers and clinicians can be confident of their findings in the RA population. Furthermore, this thesis has also confirmed that RA individuals are satisfied with the use of the tool and do not perceive it to be burdensome. Thus, this tool is closely aligned with the recommendations of Livingstone et al. (2003) for the ideal method of physical activity measurement.

2. In a similar vein, the results of this thesis have demonstrated that the frequently utilised IPAQ-SF is not a suitable tool for measurement of physical activity in the RA population. Based on these findings it is recommended to discontinue its use in this population.

3. This thesis has outlined that the measurement of TEE alone is not an ideal representation of physical activity in this population. PAEE is a better indicator as it allows for the accounting of the increased metabolic activity (increased REE) in this population. On this basis it is recommended that measurement of PAEE is taken, especially when comparisons are being made to other populations.

4. This thesis recognises that PAEE levels are decreased in the female RA population compared to a female control population. Thus, it would be recommended that interventions to increase physical activity be targeted at this population in particular. Furthermore, findings of this thesis would recommend the targeting of female, non-employed, smokers and those with higher HAQ scores as these groups represent those with greatest potential for energy expenditure increases.

5. The findings of this thesis suggest that physical activity has a role in the moderation of inflammatory markers and thus may be an important mechanism in the reduction of inflammation related cardiovascular disease risk in this population.
11.6 Recommendations for Future Research

Based on the work conducted in the creation of this PhD thesis, a number of recommendations can be made for future research to build on the findings of this work and further improve knowledge of this topic.

1. Based on the findings of the systematic review (Chapter 3) and the recommendations of Haskell et al. (2007), assessment of moderate intensity physical activity in continuous ten minute bouts would be advocated for use in future research.

2. Assessment of a wider range of potential health related correlates (e.g. pain, stiffness, fatigue) of physical activity may allow for the development for more specific targeted interventions with the aim of increasing physical activity in the RA population. Furthermore, these interventions should be assessed by prospectively designed studies to infer causality.

3. Validation of SWA ability to estimate energy expenditure during sleep and its ability to estimate basal metabolic rate to allow for more accurate imputation of sleep would strengthen the overall validity of the tool in this population.

4. A prospectively designed study would allow for determination of whether physical activity reduces inflammatory marker levels in the RA population. Furthermore if this was established, studies should be designed to determine what the appropriate physical activity dose, type and intensity is and what duration of physical activity is necessary to cause effect on inflammatory markers.

11.7 Conclusion

This PhD thesis has identified SWA in terms of its energy expenditure output as a valid measure of physical activity and has recommended its use in the measurement of habitual free living physical activity in the RA population. Furthermore, it has found SWA to be well tolerated by users who perceive it to be unobtrusive and not an imposition upon their lives. Conversely, the thesis has also determined that the frequently utilised subjective physical activity questionnaire (IPAQ-SF) is generally not appropriate for use in the RA population.
This thesis has also provided a comprehensive profile of energy expenditure in the RA population, reported on where this sits in relation to other literature in the area, how it compares to a control population and determined correlates of physical activity for this population, which may serve as indicators of how physical activity promoting interventions should be designed for this population.

Furthermore, this thesis has identified a link between energy expenditure and a number of inflammatory markers which are acknowledged to be associated to cardiovascular disease, and thus has provided opportunities to begin prospectively designed studies in this area.
CHAPTER 12 PUBLICATIONS
12.1 INTRODUCTION
This chapter describes a list of the publication output of this thesis to date, including journal publications, and oral and poster presentation at conferences.

12.2 JOURNAL PUBLICATIONS


12.3 PUBLISHED CONFERENCE PROCEEDINGS


12.4 Other Oral and Poster Conference Presentations


Hannon, J. C. (2008) 'Physical activity levels of overweight and nonoverweight high school students during physical education classes', *Journal of School Health*, 78(8), 425-431.


Hinrichs, T. and Brach, M. (2011) 'The General Practitioner's Role in Promoting Physical Activity to Older Adults: A Review Based on Program Theory', *Current aging science*.


energy expenditure in obese individuals', *Obesity (Silver Spring)*, 14(12), 2217-23.


218


APPENDICES
APPENDIX A: CRITERION VALIDITY OF SHIMMER IN RA
BACKGROUND TO SHIMMER

The SHIMMER (Sensing Health with Intelligence, Modularity, Mobility, and Experimental Reusability) wireless sensor platform has been developed by Realtime Technology in conjunction with the Intel Digital Health Group over the past number of years to support a variety of internal and external research projects. It is a small matchbox shaped instrument (approx 50mm x 25mm x 12.5mm) which is very light (15 grams) and can sample three channels of 12-bit ADC at 50Hz for up to ten days. The SHIMMER platform comprises of a baseboard which provides the sensors’ computational, data storage, communications and daughterboard connection compatibilities.

The core element of the baseboard is the MSP430 microcontroller unit (MCU). The primary advantage of this MCU is its low power consumption during periods of inactivity. The baseboard also contains a tri-axial accelerometer (Freescale Semiconductor 3-axis accelerometer MMA7260Q) and a passive tilt/vibration sensor (SQ-SEN-200-Signal Quest) (McGrath and Dishongh 2009).

For further functionality, the SHIMMER baseboard allows connection of daughterboards. These include: PIR (Passive Infra Red), ECG (Electrocardiography), EMG (Electromyography), GSR (Galvanic Skin Response), Gyroscope, Magnetometer board and a 9DoF board (combination of magnetometer/gyroscope). The SHIMMER base board also features two radios (a Bluetooth radio and a 802.15.2 radio) which can be selected depending on the application’s requirements.

The SHIMMER baseboard also features a MicroSD card slot that supports up to two GB of flash memory. This allows sensor data to be written to the MicroSD and downloaded for analysis at a later date.

SHIMMER produces output in raw data form. The MSP430 has eight channels/ports. For the SHIMMER platform, the external ports (three channels) are utilised for reading data from the accelerometer, the internal expansion connector (two channels), and the external expansion connector (two channels). All data is produced as rows of XYZ data.

At 50Hz, there are 50 data points at X, Y and Z produced each second. Likewise, at 250Hz there are 250 data points produced. The raw data output of SHIMMER is
unique and extremely helpful as it allows full control over the interpretation and analysis of the recorded event.

Algorithms are developed, designed and applied according to the need of the user and the specific population group involved.

Consequently, the uses of SHIMMER with its various daughterboards are varied and immense.

**INTRODUCTION TO STUDY**

As outlined in Chapter 5, determination of validity for physical activity measurement tools is of utmost importance in order to have confidence in the accuracy of the results of such tools.

The purpose of this study is to evaluate the criterion validity of SHIMMER located at the thigh, waist and chest to estimate 1) step count when compared to the criterion measure, manual count of steps during video observation, and 2) to estimate energy expenditure compared to the criterion measure, indirect calorimetry, during activities of daily living (ADL’s) in people with RA.

**METHODOLOGY**

Recruitment of subjects and other methodology aspects were conducted in a similar manner to that conducted for SWA and reported in Chapter 5.

SHIMMER was used in two differing manners for the current validation study. In the step count aspect of this application, the core functionality of SHIMMER was extended via a gyroscope daughterboard (InvenSense MEMs gyroscope) and the on-board accelerometer (Freescale MMA7260Q 1.5/2/4/6g MEMs accelerometer) sampled 3 channels of data. The subjects wore a SHIMMER at the waist (ShimW) and on the dominant thigh (ShimT), at the level of the iliac crests and in line with the sternum in the case of the waist location and with the lower border located 5 inches above the superior pole of the patella in the case of the thigh. These SHIMMERs sampled at a rate of 51.2Hz. In the energy expenditure aspect of the application, the SHIMMER platform utilised the accelerometer which again sampled 3 channels of data. The SHIMMER was located on the chest (ShimC) at the level of the xiphoid process. In this case the sampling frequency was 250Hz.
DATA PROCESSING
During the protocol, step count was estimated from the triaxial gyroscope signal sampling at 51.2Hz recorded by ShimW and ShimT. Steps were identified as maximum peaks in the gyroscope signal in the anterior-posterior axis which reached values above certain subject specific amplitude thresholds (Greene et al. 2010). Falsely identified steps were eliminated by discounting steps with a lower peak amplitude which occurred within half a second of another step of higher peak amplitude.

Data produced by the triaxial accelerometer ShimC sampling at 250Hz was analysed in two formats previously described by Twomey et al. (2010) in order to estimate energy expenditure. The algorithms which were applied to this data was Bouten’s linear (Bouten et al. 1994) and Chen’s non linear (Chen and Sun 1997) equations.

Bouten’s linear equation is defined as:

\[ EE_{act} = 0.104 + 0.023 \times IAA_{tot} \]

where \( EE_{act} \) is the energy expenditure estimation due to activity that the equation calculates and \( IAA_{tot} \) is a dimensionless unit know as the integral of the absolute value of the acceleration.

Chen’s non linear equation is defined as:

\[ EE_{act}(k) = \alpha_N \times H(k)^{p1} + b_N \times V(k)^{p2} \]

where:

\[ p1 = \frac{2.66 \times mass(kg) + 146.72}{1000} \]
\[ p2 = \frac{-3.85 \times mass(kg) + 968.28}{1000} \]
\[ \alpha_N = \frac{12.81 \times mass(kg) + 843.22}{1000} \]
\[ b_N = \frac{38.90 \times mass(kg) - 682.44 \times gender + 692.50}{1000} \]
where gender is defined as 1 for male and 2 for female, \( H = \sqrt{x^2 + y^2} \) and \( V = \) acceleration in the z axis.

In order to allow comparison with the gold standard Oxycon mobile measurement, data from ShimC was computed to 30 second intervals. This again was converted to energy expenditure for the relevant 5 or 10 minute activities as well as the total protocol. SHIMMER produced energy expenditure values in kcals so this was converted to kJ using the equation:

\[
1 \text{kcal} = 4.184 \text{kJ}
\]

ShimW and ShimT were compared to manual step count to assess step count agreement. This was done in terms of the total protocol and also when the protocol was divided into Class A, B and C categories. Similar analyses were conducted for ShimC compared to Oxycon mobile indirect calorimetry output to assess energy expenditure agreement.

**DATA ANALYSIS**

Fourteen subjects were recruited and performed all the activities in the protocol. Of these 14 subjects, complete data was available for 14 subjects for Oxycon, Video, ShimT, ShimC and SWA. Due to technical difficulties with ShimW, only data on 12 subjects were available for this measure and consequently analyses regarding ShimW involves 12 subjects. Statistical analysis was conducted in a similar manner to that conducted for SWA and reported in Chapter 5.

**RESULTS**

**A) STEP COUNT**

A summary of the Bland and Altman analyses comparing ShimW to manual step count is presented (Table 1) for both the total protocol and the varying intensity categories. With regard to the total activity category, the ICC for the agreement between ShimW and manual step count was 0.157 (p=0.145) suggesting poor agreement. This level of agreement was found to be similarly poor for Class A intensity (ICC=0.174, p=0.170), Class B (ICC=0.027, p=0.440) and Class C (ICC=0.031, p=0.456). The Bland and Altman plot (Fig. 1) for the total protocol reiterates this finding.
### TABLE 1 BLAND AND ALTMAN TABLE FOR STEP COUNT (SHIMMER WAIST)

<table>
<thead>
<tr>
<th>Intensity Category</th>
<th>Bland and Altman (SHIMMER Waist prediction of Step Count)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d (steps)</td>
</tr>
<tr>
<td>Total</td>
<td>455.83</td>
</tr>
<tr>
<td>Class A</td>
<td>348.50</td>
</tr>
<tr>
<td>Class B</td>
<td>124.17</td>
</tr>
<tr>
<td>Class C</td>
<td>-13.75</td>
</tr>
</tbody>
</table>

Key: d (mean differences), SE (standard error), CI (confidence interval), SD_{diff} (standard deviation of the differences), LOA (limits of agreement)

### FIGURE 1 BLAND AND ALTMAN PLOT FOR TOTAL STEP COUNT (SHIMMER WAIST)

![Bland and Altman Plot for Total Step Count](image-url)
Again, a summary of the Bland and Altman analyses comparing ShimT to manual step count is presented (Table 2) for both the total protocol and the intensity categories and the total Bland and Altman plot is also presented. For the total activity category, ShimT demonstrated an ICC of 0.878 (p<0.0001) which is considered almost perfect agreement and a correlation coefficient of 0.900 (p<0.0001), which is considered strong with manual step counts. The Bland and Altman plot for ShimT (Fig 2) suggests that ShimT tends to underestimate steps for the total protocol. Bland and Altman analyses also demonstrate this with a mean difference of 95.13 steps and 95% CI: of -4.84, 193.70. The ICC values for the agreement between ShimT and manual step counts for Class A, B and C are 0.920 (p<0.0001), 0.558 (p=0.005) and 0.379 (p=0.019) respectively. Correlation coefficients for the same three variables were demonstrated as 0.933 (p<0.0001), 0.749 (p=0.002) and 0.621 (p=0.018) respectively. Similar to findings for the total activity category, Bland and Altman analyses for ShimT tends to underestimate for Class A and B categories, having mean differences and associated 95% confidence intervals of 58.57 (95%CI: -13.83, 130.97) and 53.93 (95%CI: 10.16, 97.70) respectively. However in the case of the low intensity category (Class C), ShimT tends to overestimate step counts with a mean difference of -15.79 (95%CI: -24.95, -6.62).
TABLE 2 BLAND AND ALTMAN TABLE FOR STEP COUNT (SHIMMER THIGH)

<table>
<thead>
<tr>
<th>Intensity Category</th>
<th>Bland and Altman (SHIMMER Thigh prediction of Step Count)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d (steps)</td>
</tr>
<tr>
<td>Total</td>
<td>96.21</td>
</tr>
<tr>
<td>Class A</td>
<td>58.57</td>
</tr>
<tr>
<td>Class B</td>
<td>55.71</td>
</tr>
<tr>
<td>Class C</td>
<td>-15.79</td>
</tr>
</tbody>
</table>

Key: d (mean differences), SE (standard error), CI (confidence interval), SD_{diff} (standard deviation of the differences), LOA (limits of agreement)

FIGURE 2 BLAND AND ALTMAN PLOT FOR TOTAL STEP COUNT (SHIMMER THIGH)
B) ENERGY EXPENDITURE

With regard to the total activity category, the agreement between ShimC (Boutens) and Oxycon was considered poor (ICC = 0.019, p=0.383). Bland and Altman analysis shows a mean difference of 571.42kJ, a standard error of 76.87kJ and a standard deviation of the difference of 287.61. When assessing the different classes of intensity, similarly poor ICC agreement between ShimC (Boutens) and manual step count for Class A (ICC=0.023, p=0.361), Class B (ICC=0.051, p=0.228) and Class C (ICC=-0.025, p=0.638) was demonstrated. These findings are displayed in Table 3 and Figure 3.

TABLE 3 BLAND AND ALTMAN TABLE FOR ENERGY EXPENDITURE (SHIMMER CHEST (BOUTENS))

<table>
<thead>
<tr>
<th>Intensity Category</th>
<th>Bland and Altman (SHIMMER Chest (Boutens) prediction of Energy Expenditure)</th>
<th>d (kJ)</th>
<th>SE of d (kJ)</th>
<th>95% CI for d (kJ)</th>
<th>SD_{diff} (kJ)</th>
<th>95% LOA (kJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>571.42</td>
<td>76.87</td>
<td>(405.36 → 737.48)</td>
<td>287.61</td>
<td>(7.70 → 1134.14)</td>
</tr>
<tr>
<td>Class A</td>
<td></td>
<td>256.84</td>
<td>35.06</td>
<td>(181.09 → 332.59)</td>
<td>131.19</td>
<td>(-0.29 → 513.97)</td>
</tr>
<tr>
<td>Class B</td>
<td></td>
<td>215.69</td>
<td>28.92</td>
<td>(153.22 → 278.16)</td>
<td>108.20</td>
<td>(3.62 → 427.76)</td>
</tr>
<tr>
<td>Class C</td>
<td></td>
<td>85.22</td>
<td>13.65</td>
<td>(55.74 → 114.71)</td>
<td>51.07</td>
<td>(-14.88 → 185.32)</td>
</tr>
</tbody>
</table>

Key: d (mean differences), SE (standard error), CI (confidence interval), SD_{diff} (standard deviation of the differences), LOA (limits of agreement)
A summary of Bland and Altman analyses comparing manual step count to ShimC (Chen) are demonstrated in Table 4 and the Bland and Altman plot (Fig 4). In terms of agreement between ShimC (Chen) and manual step count, the ICC for the total activity category was 0.068 (p=0.179). For Class A, the ICC was 0.030 (p=0.379), for Class B, this was 0.129 (p=0.063) and for Class C, it was 0.082 (p=0.021), again indicating poor agreement. However correlational analysis of ShimC (Chen) were found to be 0.735 (p=0.003), 0.205 (p=0.481), 0.773 (p=0.001) and 0.640 (p=0.014) for total, Class A, Class B and Class C respectively.
## TABLE 4 BLAND AND ALTMAN TABLE FOR ENERGY EXPENDITURE (SHIMMER CHEST (CHEN))

<table>
<thead>
<tr>
<th>Intensity Category</th>
<th>Bland and Altman (SHIMMER Chest (Chen) prediction of Energy Expenditure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d (kJ)</td>
</tr>
<tr>
<td>Total</td>
<td>492.72</td>
</tr>
<tr>
<td>Class A</td>
<td>189.41</td>
</tr>
<tr>
<td>Class B</td>
<td>182.51</td>
</tr>
<tr>
<td>Class C</td>
<td>118.08</td>
</tr>
</tbody>
</table>

Key: d (mean differences), SE (standard error), CI (confidence interval), SD$_{diff}$ (standard deviation of the differences), LOA (limits of agreement)
DISCUSSION
This study has determined that ShimW is not valid to estimate step counts after analysis with by ICC, Bland and Altman and correlational methods.

The computed ICC values for the agreement ShimW and manual step count represent poor agreement and do not inspire confidence that SWA is a valid tool for predicting step counts in this population. The Bland and Altman analyses also show poor agreement between ShimW and manual step counts. The mean difference of 455.83 steps or the total activity category in a 75 minute protocol must be considered in the larger context of a 24 hour day or indeed 7 day week.

With regard to ShimT, although the ICC, Bland and Altman and correlational analyses for the total activity category and Class A category are particularly strong and would indicate validity, the analyses conducted for Class B and in particular Class C are less indicative of validity.

The reason for this discrepancy in ability to distinguish steps at differing intensities stems from the step count algorithms used on the SHIMMER raw data (Greene et al. 2010). These algorithms have a strong ability to determine steps when foot contact with the ground is great, as in higher intensity activities (walking, stair climbing,
cleaning) but less accurate in lower intensity activities when clear stepping motion tends not occur and amplitude of the gyroscope angular velocity signal is lessened. Furthermore, the variability of step intensity also plays a role. The size or amplitude of steps taken during more intense activities (walking, stair climbing) tend to be more consistent than lesser intense activities (dressing, folding laundry).

Therefore, if subjects were participating mainly in activities with definite step motion, this tool appears to accurately represent these tasks. However, activities with less definite stepping motion appear not be represented accurately.

Furthermore, the ability of the algorithms which are used to determine step count for ShimT are currently unable to be utilised for a longer period than the 75 minute protocol, and thus this tool may not be suitable in its current form to measure habitual free living physical activity.

The utilisation of two algorithms with ShimC were not successful in providing a valid measure of energy expenditure in the RA population. These algorithms have been devised for use with SHIMMER to accurately determine energy expenditure (Twomey et al. 2010). However, with regard to the determination of the validity of SHIMMER to estimate energy expenditure in this population these algorithms appear not to perform as well as they did in the healthy, younger population. It is likely that physiological differences as well as demographical differences between the RA and non RA populations account in some part for these inaccuracies as this was found to be the case when determining resting energy expenditure algorithms (Metsios et al. 2008a). Furthermore, the placement site differed in this application to that of Twomey et al. (2010). Although ShimC (Chen) did show large strength correlations for the total activity category (r=0.735, p=0.003), Class B category (r=0.773, p=0.001) and Class C category (r=0.640, p=0.014), the accuracy was poor, as demonstrated by both ICC and Bland and Altman analyses. Thus, despite there being a strong linear association, the differences between the criterion measure (Oxycon) and ShimC (Chen) are of a large magnitude.

**IMPLICATIONS**

It is recommended that SHIMMER would not be used with the current algorithms to estimate energy expenditure in this population, however if the ability of ShimT to
record step count for a longer duration could be improved on there is scope for it to be utilised as a measurement tool in this population, with consideration paid to its tendency to underestimate step counts.

CONCLUSION
SHIMMER cannot be considered a valid tool to estimate energy expenditure, and due to the difficulties in utilising SHIMMER (Thigh) for periods of longer duration, there is very limited scope for its use in its current form to measure free living physical activity in this population.
APPENDIX B: MODIFIED NEWCASTLE OTTAWA SCALE
Based on Newcastle-Ottawa scale (available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) and modified Newcastle-Ottawa scale used by Smedslund and Birger Hagen 2010.

1. Representativeness
   1.1. Sample is truly representative of the average patient with Rheumatoid Arthritis

2. Ascertainment of exposure
   2.1. Physical activity was adequately measured and participants were exposed to a variety of physical activity opportunities

3. Subjects blinded to study aims
   3.1. The participants were not informed that physical activity levels / energy expenditure levels would be recorded

4. Duration covering full range of variation
   4.1. Recorded levels for at least one week is preferred but recordings covering at least 2 weekdays AND 1 weekend day, i.e. periods with substantial variation, are acceptable.

5. Diagnosis
   5.1. Participants have a formal diagnosis of Rheumatoid Arthritis according to the ACR criteria (Arnett et al. 1988).

6. As autocorrelations were not relevant in all of the included studies, the changing of the wording of the following criteria was deemed necessary

7. Adequate use of statistics
   7.1. Statistical analysis is clearly described and appropriate

8. Attrition
   8.1. Complete follow up of all subjects or subjects lost to follow up are unlikely to introduce bias: number lost less than 20%

9. The use of studies with controls did occur in the conducting of this review, thus inclusion of a methodology quality criteria relating to this was deemed relevant.

10. Comparability
    10.1. Participants and controls are adequately comparable in terms of health status (differing) AND age and gender (similar).
APPENDIX C: INFORMATION SHEETS, CONSENT FORMS AND INFORMATION BOOKLET AND DIARY
An investigation to validate the SHIMMER and SWA in a Rheumatoid Arthritis population

SUBJECT INFORMATION SHEET

The information below explains why this study is being carried out and also what it involves. Please take some time to read it. If you have any further questions please ask the investigator

Introduction:
The SHIMMER is a new device that can measure the physical activity level and heart rate of an individual. It is a small, matchbox sized wireless box which is worn on a strap or attached using adhesive tape. The SenseWear Armband is a commercially available physical activity monitor which is worn on a Velcro strap on the upper arm. Both been used in a variety of populations but not in a Rheumatoid Arthritis population so we want to assess if it is applicable in this population

Procedures (What will happen?):
Before coming for testing you will be asked not to eat for four hours and not have drank alcohol or participated in exercise for 24 hours. Before starting the study, you will be asked to fill out a questionnaire about your physical activity. We will take your weight and height. We will then apply one SHIMMER around your waist, one to your thigh and one to your chest. We will also apply a heart rate monitor around your chest, the SWA on your upper arm and ask you to wear a facemask which will measure the air you breathe out. You will then be asked to lie on your back and rest for 30 minutes. Then you will be asked to complete 8 tasks, each for 10 minutes, with the exception of one activity (stair climbing) which will last for 5 minutes. These activities are ones you commonly perform daily and are: dressing, walking, reading, cleaning/washing delf, stair climbing, computer work / writing, cleaning surfaces and folding laundry. At any time during any of the activities you can stop and rest if you become fatigued. After you have completed the activities, the equipment will then be taken off and you will be asked to remain in the testing area for 10 minutes.

What are the benefits/risks?
Benefits:
There are no immediate benefits to be gained from the study. However the data that will be collected from your participation will be used to determine if the SHIMMER and SWA can be used to measure physical activity in the rheumatoid arthritis population. You will also have the opportunity to be part of a longer-term study, aiming to assess the link between physical activity and cardiovascular health.

Risks:
There are no potential serious risks to you. There is a minimal risk of falling during physical activity. This will be minimised by continuous supervision during testing by a Chartered Physiotherapist and performance of activities that you complete daily
There is a minimal risk of discomfort due to wearing of facemask. This will be minimised by sizing and fitting the facemask for you individually. There is a minimal risk of infection due to wearing of the facemask. The facemask will be thoroughly cleaned and disinfected after each person’s use. A Chartered Physiotherapist will be on site during the testing to ensure your safety, and a first aid box will also be available.

**Exclusion from participation:**
Unfortunately, you cannot participate in this study if you are under the age of 18. Unfortunately, you also cannot participate if you are currently experiencing a flare up in your condition or are pregnant.

**Confidentiality:**
All information collected in this study will remain strictly confidential, and data gathered will be used for statistical purposes only.

**Voluntary Participation:**
Participation in this study is entirely voluntary.

**Stopping the study:**
Should you wish to withdraw from the study at any time, you are free to do so. You may have your data withdrawn from the study at any time also.

**Permission:**
We need your permission to use the data that we will receive from your participation in the study. When you are finished reading this information sheet we will ask you to sign a consent form for us to use the data.

**Complaints procedures:**
If you have any concerns about this project and wish to contact an independent person, please feel free to contact:

The Chairman  
Scientific Research Ethics Committee  
Limerick Regional Hospital, Dooradoyle, Limerick

**Further information**
If you have any further queries or if there is anything you don’t understand, you can ask me now or contact me at:

Marie Tierney  
Dept of Physiotherapy,  
University of Limerick,  
Limerick.  
Email: marie.tierney@ul.ie  
Tel: (087) 2XXXXXX

The other investigators involved in this study are  
Dr. Alexander Fraser, Rheumatology Dept, Mid Western Regional Hospitals and  
Dr. Norelee Kennedy, Dept of Physiotherapy, University of Limerick.
Title of project: An investigation to validate the SHIMMER and SWA in a Rheumatoid Arthritis population.

Informed Consent Form

Please read the following questions and tick the boxes that apply to you:

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<td>I give my permission for the investigator to inform my GP of my participation in this study</td>
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**SIGNATURE**                  **BLOCK CAPITALS**                  **DATE**

Subject: __________________   ___________________          ___________

Investigator: _______________ ___________________         ___________

Witness: _______________ ___________________          ___________
AN INVESTIGATION TO ASSESS THE LEVELS OF PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS AND ASSESS RELATIONSHIP BETWEEN LEVELS OF PHYSICAL ACTIVITY AND INFLAMMATION RELATED CARDIOVASCULAR HEALTH

SUBJECT INFORMATION SHEET

The information below explains why this study is being carried out and also what it involves. Please take some time to read it. If you have any further questions please ask the investigator

Introduction:
We want to assess the levels of physical activity in individuals with Rheumatoid Arthritis, compare that with others who do not have Rheumatoid Arthritis and also see if your level of physical activity has any effect on some blood tests, which affect cardiovascular health. We will measure how much physical activity you do by use of a Sensewear Armband and a SHIMMER. The Sensewear Armband is a monitor worn on a strap on your upper arm. SHIMMER is a small matchbox sized piece of equipment which is worn on your thigh.

Procedures (What will happen?):
If you express an interest in taking part in this study:
- A SHIMMER will be placed on your thigh and a Sensewear on your upper arm for 7 days. Only remove these when going to bed at night and in water based activities (bathing, showering, and pool activities). You will be shown how to properly put on/take off the devices. You will also need to keep a diary of the times you removed either device.
- You should just continue with your normal activities during the 7 day period.
- A blood sample will be taken at the start of the 7 day period by a person qualified to do this.
- Your blood pressure, the number of tender and swollen joints and a questionnaire detailing your address, telephone number, date of birth, weight, height, whether you are a smoker or non-smoker, right or left handedness as well as some details regarding your rheumatoid arthritis and other medical history will be recorded. Access to your medical charts may be necessary to get further information on these details.
- The physical activity monitors will be returned at the end of the 7 day period and some aspects of the questionnaire will be repeated.
- Much of the work to determine the results of the study will be conducted at the Dept. of Physiotherapy, University of Limerick. Data will be held on file in the University of Limerick for 7-10 years as is normal to allow for it to be maximally analysed.

What are the Benefits:
- After the study is completed you can be provided with an assessment of your physical activity levels.
- Special blood samples which are not taken routinely and have to be sent to Dublin for analysis will be taken as part of this research study. These will be made available to your rheumatology team at the end of this study.

What are the Risks:
- Irritation due to use of tape and Velcro however this is unlikely to occur as these monitors have been used previously with no adverse effect. If you experience any adverse effects you should remove the monitor.
- You may feel self-conscious or embarrassed wearing the devices. However, these are small, easily concealable devices. SHIMMER is a matchbox sized tool worn on the thigh, while SWA is small monitor worn on the upper arm. Again you can remove both/either monitor if you wish.
- Excessive bleeding or bruising associated with the blood sampling. However, as an individual certified in phlebotomy will conduct all sampling this is unlikely to occur.
- Fainting/light-headedness due to blood sampling. This is unlikely to occur as only 10 mls of blood will be taken.
- Infection related to blood sampling. Again this is unlikely to occur due to antiseptic practices employed by the certified phlebotomist.

**Exclusion from participation:**
You cannot participate if you are under the age of 18 or if you are currently pregnant.

**Confidentiality:**
All information collected in this study will remain strictly confidential, and data gathered will be used for statistical purposes only. Your data will be available only to Marie Tierney, Dr. Alexander Fraser and Dr. Norelee Kennedy.

**Voluntary Participation and Stopping the study**
Participation in this study is entirely voluntary and your decision will not impact your care. Your normal care will continue throughout the duration of this study. Should you wish to withdraw from the study at any time, you are free to do so. You may have your data withdrawn from the study at any time also. This will not impact your care in any way.

**Permission:**
I need your permission to use the data that will be received from your participation in the study. When you are finished reading this information sheet I will ask you to sign a consent form for us to use the data.

**Complaints procedures:**
If you have any concerns about this project and wish to contact an independent person, please feel free to contact:

*The Chairman*
Scientific Research Ethics Committee
Limerick Regional Hospital, Dooradoyle, Limerick

**Further information**
If you have any further queries or if there is anything you don’t understand, you can ask me now or contact me at:
Marie Tierney, Dept of Physiotherapy, University of Limerick, Limerick.
Email: marie.tierney@ul.ie
Tel: (087) 2XXXXXX

The other investigators involved in this study are
Dr. Alexander Fraser, Rheumatology Dept, Mid Western Regional Hospitals
and
Dr. Norelee Kennedy, Dept of Physiotherapy, University of Limerick.

*Maria Tierney is sponsored in the form of a scholarship from the Irish Research Council for Science Engineering and Technology in conjunction with Intel Ireland. Neither of these companies will have access to any personal data or individual results produced by this study.*
AN INVESTIGATION TO ASSESS THE LEVELS OF PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS AND ASSESS RELATIONSHIP BETWEEN LEVELS OF PHYSICAL ACTIVITY AND INFLAMMATORY RELATED CARDIOVASCULAR HEALTH

**Informed Consent Form**

Please read the following questions and tick the boxes that apply to you:

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**Signature**

Subject: ___________________  ___________________  ___________

Investigator: ___________________  ___________________  ___________
AN INVESTIGATION TO ASSESS THE LEVELS OF PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS COMPARED TO DISEASE CONTROLS

CONTROL SUBJECT INFORMATION SHEET

The information below explains why this study is being carried out and also what it involves. Please take some time to read it. If you have any further questions please ask the investigator.

**Introduction:**
We want to assess the levels of physical activity in individuals with Rheumatoid Arthritis, compare that with others who do not have Rheumatoid Arthritis. We will measure how much physical activity you do by use of a Sensewear Armband and a SHIMMER. The Sensewear Armband is a monitor worn on a strap on your upper arm. SHIMMER is a small matchbox sized piece of equipment which is worn on your thigh.

**Procedures (What will happen?):**
If you express an interest in taking part in this study:
- A SHIMMER will be placed on your thigh and a Sensewear on your upper arm for 7 days. Only remove these when going to bed at night and in water based activities (bathing, showering, and pool activities). You will be shown how to properly put on/take off the devices. You will also need to keep a diary of the times you removed either device.
- You should just continue with your normal activities during the 7 day period.
- A questionnaire detailing your address, telephone number, date of birth, weight, height, whether you are a smoker or non-smoker, and right or left handedness will be recorded. Access to your medical charts may be necessary to get further information on these details.
- I will come to your house to pick up the equipment when the test is over or if it suits you we can arrange a convenient other location.
- Much of the work to determine the results of the study will be conducted at the Dept. of Physiotherapy, University of Limerick. Data will be held on file in the University of Limerick for 7-10 years as is normal to allow for it to be maximally analysed.

**What are the benefits:**
After the study is completed you can be provided with an assessment of your physical activity levels.

**What are the risks:**
- Irritation due to use of tape and Velcro however this is unlikely to occur as these monitors have been tested and used previously with no adverse effect. If you experience any adverse effects you should remove the monitors.
- You may feel self-conscious or embarrassed wearing the devices. However, these are small, easily concealable devices. SHIMMER is a matchbox sized tool worn on the thigh, while SWA is small monitor worn on the upper arm. Again you can remove both/either monitor if you wish.

**Exclusion from participation:**
You cannot participate in this study:
- If you are under the age of 18.
• If you are pregnant.
• If you have rheumatoid arthritis or other inflammatory arthritis

Confidentiality:
All information collected in this study will remain strictly confidential, and data gathered will be used for statistical purposes only. Your data will be available only to Marie Tierney, Dr. Alexander Fraser and Dr. Norelee Kennedy.

Voluntary Participation and Stopping the study:
Participation in this study is entirely voluntary and your decision will not impact your care. Your normal care will continue throughout the duration of this study. Should you wish to withdraw from the study at any time, you are free to do so. You may have your data withdrawn from the study at any time also. This will not impact your care in any way.

Permission:
We need your permission to use the data that we will receive from your participation in the study. When you are finished reading this information sheet we will ask you to sign a consent form for us to use the data.

Complaints procedures:
If you have any concerns about this project and wish to contact an independent person, please feel free to contact:

The Chairman
Scientific Research Ethics Committee
Limerick Regional Hospital, Dooradoyle, Limerick

Further information
If you have any further queries or if there is anything you don’t understand, you can ask me now or contact me at:

Marie Tierney, Dept of Physiotherapy, University of Limerick, Limerick.
Email: marie.tierney@ul.ie
Tel: (087) 2XXXXXX

The other investigators involved in this study are
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AN INVESTIGATION TO ASSESS THE LEVELS OF PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS COMPARED TO DISEASE CONTROLS

**Informed Consent Form**

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**Signature**

Subject: ___________________  ___________________  ___________

Investigator: ___________________  ___________________  ___________

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**Date**

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AN INVESTIGATION TO ASSESS THE OPINION OF WEARING A PHYSICAL ACTIVITY MONITOR IN THE HOME IN THE RHEUMATOID ARTHRITIS POPULATION

SUBJECT INFORMATION SHEET

The information below explains why this study is being carried out and also what it involves. Please take some time to read it. If you have any further questions please ask the investigator

Introduction:
We want to assess how you perceived the wearing of a physical activity monitor in the home. We will aim to do this in the form of two focus groups. Approximately, 5 other people who have rheumatoid arthritis and who also wore the physical activity monitor will be present along with myself and another researcher. I will ask a couple of questions about your thoughts on it and you and the other participants can discuss these topics if you like.

Procedures (What will happen?):
If you express an interest in taking part in this study, please return the consent form (enclosed with this letter) in the stamped addressed envelope provided.
I will then contact you to let you know if you have been selected to take part and advise you where the location of the focus group. It will be held in a location which is in your locality.

On the day:
- You will be asked to sign a consent form.
- A number of questions relating to the wearing of the physical activity monitor will be asked to you and the other participants which a discussion may ensue from.
- The entire discussion will be tape recorded to allow for analysis of what was said.
- Another research student will also be present to take notes
- You do not have to answer any questions or take part in discussion that you do not feel comfortable doing.

After the focus group:
- A copy of the main points discussed within the group will be sent to you for checking to see if you agree with analysis of the main points which were raised.
- Much of the work to determine the results of this study will be conducted at the Dept. of Physiotherapy, University of Limerick.
- The data will be held on file in the University of Limerick for 7-10 years as is normal to allow for it to be maximally analysed.

What are the benefits:
You can have your say on what you felt it was like to have worn a physical activity for 7 days.
What are the risks:
You may feel uncomfortable sharing opinions during the focus group. However, you can express as much or as little as they wish within the group and are under no obligation to disclose anything which you do not wish you

Exclusion from participation:
Once you have rheumatoid arthritis and participated in the study in which you wore the physical activity monitor you can participate

Confidentiality:
All information collected in this study will remain strictly confidential, and data gathered will be used for statistical purposes only. Your data will be available only to Marie Tierney, Dr. Alexander Fraser and Dr. Norelee Kennedy.

Voluntary Participation and Stopping the study:
Participation in this study is entirely voluntary and your decision will not impact your care in any way. Your normal care will continue throughout the duration of this study. Should you wish to withdraw from the study at any time, you are free to do so. You may have your data withdrawn from the study at any time also.

Permission:
We need your permission to use the data that we will receive from your participation in the study. When you are finished reading this information sheet we will ask you to sign a consent form for us to use the data.

Complaints procedures:
If you have any concerns about this project and wish to contact an independent person, please feel free to contact:

The Chairman
Scientific Research Ethics Committee
Limerick Regional Hospital, Dooradoyle, Limerick

Further information
If you have any further queries or if there is anything you don’t understand, you can ask me now or contact me at:

Marie Tierney, Dept of Physiotherapy, University of Limerick, Limerick.
Email: marie.tierney@ul.ie
Tel: (087) 2XXXXXX

The other investigators involved in this study are
Dr. Alexander Fraser, Rheumatology Dept, Mid Western Regional Hospitals
and
Dr. Norelee Kennedy, Dept of Physiotherapy, University of Limerick.

Marie Tierney is sponsored in the form of a scholarship from the Irish Research Council for Science Engineering and Technology in conjunction with Intel Ireland. Neither of these companies will have access to any personal data or individual results produced by this study.
AN INVESTIGATION TO ASSESS THE OPINION OF WEARING A PHYSICAL ACTIVITY MONITOR IN THE HOME IN THE RHEUMATOID ARTHRITIS POPULATION

Informed Consent Form

Please read the following questions and tick the boxes that apply to you:

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<td>Investigator:</td>
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Application of Monitors:

Sensewear:

The Senserwear armband is designed to be worn on the back of the upper right arm (the tricep muscle), touching the skin. The timestamp button is located near the top of the armband. Slide the Sensewear armband onto your right arm with the timestamp button facing up. Adjust the strap so that it fits on your arm comfortably, then secure the oval pull tab. Ensure that the sensors maintain continuous contact you’re your skin at all times and that the armband does not slide off your arm.

Be careful not to secure the armband too tightly. If your arm begins to tingle or you begin to lose feeling in your arm, loosen the adjustable strap and re-fasten. Once the strap fits your arm comfortably, there is no need to readjust it every time you put it on and off.
Simply slide it on and off of your arm. There is no on/off button on your Sensewear armband. When the monitor makes secure contact with your body, it automatically performs a “turning on” sequence. This may take up to five minutes for some people. The sequence is as follows:

**Welcome:** Four distinct notes (do-de-do-deet) ascending in tone. This sound indicates that the Sensewear armband has made contact with your skin.

**Warming up:** Two second vibration. You’ll feel a series of light vibrations as it settles to your body.

**Ready:** Three notes (de-de-deet). This sound indicates that the armband is collecting data.

If, after five minutes, you do not hear the “turning on” sequence or you think you may have missed it, press and hold the timestamp button until you hear the “ready” sound, which means that your Sensewear armband is working properly.
**SHIMMER:**

SHIMMER is worn on the dominant upper thigh – approx 5 inches above the knee. The sticker on the SHIMMER should face outwards and with the up (↑) arrow facing upwards. Tape the SHIMMER into place with the tape provided and then cover with bandage supplied. There is no on/off button on the SHIMMER. However, the SHIMMER will **NOT** beep when it has been put on.

Do not wrap the tape around the entire leg. Instead just tape the SHIMMER onto the front of the leg and then cover with bandage to ensure it stays in place.
Removal of monitors:

When should monitors be removed?

- Monitors should be removed for showering, bathing, swimming etc.
- Monitors can be removed at night if you wish to do so. If you do not remove them at night, be sure to check position in the morning. New tape should be applied to SHIMMER each day.

How to remove:

Sensewear:

There is no need to readjust it every time you put it on and off. Simply slide it on and off of your arm.

SHIMMER:

Remove bandage. Remove tape and SHIMMER. Tape CANNOT be reused again.

Diary:

It is necessary for us to know when you removed Sensewear and the reason why you did so (bed, shower, swimming etc.) and when you re-applied it.

For this reason you have been supplied with a basic diary to keep note.

Please be as accurate with the times as possible.

Example diary entry:

Time on: 8.20am, Had shower at 7.45pm. Off at 7.45pm, back on at 7.55pm. Time off for bed: 10.40pm.
If at any time, you have any adverse reactions to either of the monitors remove immediately and do not re-apply.

If you have any queries during or after the study, please contact Marie Tierney at (087) 2402099 or marie.tierney@ul.ie.
APPENDIX D: DATA COLLECTION FORM (TENDER COUNT, SWOLLEN COUNT, VISUAL ANALOG SCALE AND HEALTH ASSESSMENT QUESTIONNAIRE)
Tender Joint Count

| R | L |

Swollen Joint Count

| R | L |

Visual Analog Scale (VAS)

How is your health presently. Please indicate by marking the line.
HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)

Name: ___________________________ Date: ________________

Please place an “x” in the box which best describes your abilities OVER THE PAST WEEK:

DRESSING & GROOMING

Are you able to:

- Dress yourself, including shoelaces and 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 own meat? [ ] [ ] [ ] [ ]
- Lift a full cup or glass to your mouth? [ ] [ ] [ ] [ ]
- Open a new 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 of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.) ☐ Built up or special utensils ☐ Crutches
☐ Special or built up chair ☐ Cane ☐ Wheelchair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking
Please place an “x” in the box which best describes your abilities OVER THE PAST WEEK:

<table>
<thead>
<tr>
<th>HYGIENE</th>
<th>WITHOUT ANY DIFFICULTY</th>
<th>WITH SOME DIFFICULTY</th>
<th>WITH MUCH DIFFICULTY</th>
<th>UNABLE TO DO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wash and dry your body?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Take a tub bath?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Get on and off the toilet?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REACH</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reach and get down a 5 pound object (such as a bag of sugar) from above your head?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Bend down to pick up clothing from the floor?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRIP</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open car doors?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Open previously opened jars?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Turn faucets on and off?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACTIVITIES</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you able to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run errands and shop?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Get in and out of a car?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Do chores such as vacuuming or yard work?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach
☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores
APPENDIX E: INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE SHORT FORM (IPAQ-SF)
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ days per week

   □ No vigorous physical activities ➔ Skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?

   _____ hours per day
   _____ minutes per day

   □ Don't know/Not sure

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ days per week

   □ No moderate physical activities ➔ Skip to question 5
4. How much time did you usually spend doing moderate physical activities on one of those days?
   _____ hours per day
   _____ minutes per day
   □ Don’t know/Not sure

   Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?
   _____ days per week
   □ No walking ➔ Skip to question 7

6. How much time did you usually spend walking on one of those days?
   _____ hours per day
   _____ minutes per day
   □ Don’t know/Not sure

   The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the last 7 days, how much time did you spend sitting on a week day?
   _____ hours per day
   _____ minutes per day
   □ Don’t know/Not sure

   This is the end of the questionnaire, thank you for participating.
Example of Statistics used in Chapter 5

Descriptives SWA (Energy Expenditure)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Statistic</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference Oxygen Loss</td>
<td>38.6079</td>
<td>7.58194</td>
</tr>
<tr>
<td>SWA Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
</tr>
<tr>
<td>for Mean</td>
<td>20.2231</td>
<td>52.9575</td>
</tr>
<tr>
<td>5% Trimmed Mean</td>
<td>30.7320</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>34.1850</td>
<td></td>
</tr>
<tr>
<td>Variance</td>
<td>804.902</td>
<td></td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>20.36303</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>-14.79</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>86.78</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>100.55</td>
<td></td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>48.84</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
<td>-.028</td>
<td>.597</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>-.539</td>
<td>1.154</td>
</tr>
</tbody>
</table>

ICC – SWA (Steps)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intraclass Correlation</th>
<th>95% Confidence Interval</th>
<th>F Test with True Value 0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
</tr>
<tr>
<td>Single Measures</td>
<td>.304</td>
<td>-.120</td>
<td>.585</td>
</tr>
<tr>
<td>Average Measures</td>
<td>.466</td>
<td>-.274</td>
<td>.813</td>
</tr>
</tbody>
</table>

Two-way mixed effects model where people effects are random and measures effects are fixed.

- Type A intraclass correlation coefficients using an absolute agreement definition.
- The estimator is the same, whether the interaction effect is present or not.
- This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Pearsons Correlation Coefficient – SWA (Energy Expenditure)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Oxygen</th>
<th>SWA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Pearson Correlation</td>
<td>1</td>
<td>.852***</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>SWA Pearson Correlation</td>
<td>.652</td>
<td>1</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

*** Correlation is significant at the 0.01 level (2-tailed).
Example of Statistics used in Chapter 7

Descriptives: TEE by employment status

<table>
<thead>
<tr>
<th>Employment</th>
<th>Statistic</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Employed</td>
<td>Mean 7.6535</td>
<td>.02943</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>Lower Bound 7.6001</td>
<td>Upper Bound 7.7180</td>
</tr>
<tr>
<td>6% Trimmed Mean</td>
<td>7.6596</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.6537</td>
<td></td>
</tr>
<tr>
<td>Variance</td>
<td>.035</td>
<td></td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>1.9073</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>7.28</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>8.01</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>.30</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
<td>.075 .386</td>
<td></td>
</tr>
<tr>
<td>Kurtosis</td>
<td>-.751 .717</td>
<td></td>
</tr>
</tbody>
</table>

Employed Mean 7.8909 .05599
95% Confidence Interval for Mean 7.7722 .00995
5% Trimmed Mean 7.8834
Median 7.9160
Variance .053
Std. Deviation 2.3097
Minimum 7.49
Maximum 8.32
Range .82
Interquartile Range .36
Skewness -.092 .550
Kurtosis -.569 1.063

Independent t-test: TEE on weekdays versus weekend days

<table>
<thead>
<tr>
<th>Independent Samples Test</th>
<th>Levene’s Test for Equality of Variances</th>
<th>Test for Equality of Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Sig.</td>
<td>t</td>
</tr>
<tr>
<td>---</td>
<td>------</td>
<td>---</td>
</tr>
<tr>
<td>LTTEE</td>
<td>.526</td>
<td>.597</td>
</tr>
<tr>
<td>Equal variances assumed</td>
<td>Equal variances not assumed</td>
<td></td>
</tr>
</tbody>
</table>

Independent t-test: PAEE of RA population versus control population

<table>
<thead>
<tr>
<th>Independent Samples Test</th>
<th>Levene’s Test for Equality of Variances</th>
<th>Test for Equality of Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Sig.</td>
<td>t</td>
</tr>
<tr>
<td>---</td>
<td>------</td>
<td>---</td>
</tr>
<tr>
<td>LightPAEE</td>
<td>6.095</td>
<td>.010</td>
</tr>
<tr>
<td>Equal variances assumed</td>
<td>Equal variances not assumed</td>
<td></td>
</tr>
</tbody>
</table>
Pearson’s Correlation Coefficient: TEE and Age

<table>
<thead>
<tr>
<th></th>
<th>LnTEE</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnTEE</td>
<td>Pearson Correlation</td>
<td>1</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Age</td>
<td>Pearson Correlation</td>
<td>- .516**</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>59</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).

Stepwise Multiple Regression: PAEE

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.618a</td>
<td>.362</td>
<td>.371</td>
<td>7.33061</td>
</tr>
<tr>
<td>2</td>
<td>.737b</td>
<td>.544</td>
<td>.527</td>
<td>6.36146</td>
</tr>
<tr>
<td>3</td>
<td>.774c</td>
<td>.698</td>
<td>.577</td>
<td>6.02199</td>
</tr>
<tr>
<td>4</td>
<td>.795d</td>
<td>.632</td>
<td>.605</td>
<td>5.81861</td>
</tr>
</tbody>
</table>

a. Predictors: (Constant), Gender
b. Predictors: (Constant), Gender, Employment
c. Predictors: (Constant), Gender, Employment, Smoking
d. Predictors: (Constant), Gender, Employment, Smoking, A/HAG
e. Dependent Variable: SqR(PAEE)
Example of Statistics used in Chapter 8

Pearsons Correlation Coefficients: ESR and Energy Expenditure variables

<table>
<thead>
<tr>
<th></th>
<th>LnESR</th>
<th>LnTEE</th>
<th>SqEEPAEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnESR Pearson Correlation</td>
<td>1</td>
<td>-0.454*</td>
<td>-0.490**</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>59</td>
<td>59</td>
<td>59</td>
</tr>
</tbody>
</table>

* Correlation is significant at the 0.01 level (2-tailed).
** Correlation is significant at the 0.00 level (2-tailed).

Hierarchial Multiple Regression: Model 1 (Age, BMI, Smoking Status) for PAEE for ESR

<table>
<thead>
<tr>
<th>Model</th>
<th>$R$</th>
<th>$R^2$</th>
<th>$R^2$ Change</th>
<th>Change Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.508</td>
<td>.256</td>
<td>.103</td>
<td>$t$ Change</td>
</tr>
<tr>
<td>2</td>
<td>.322</td>
<td>.103</td>
<td>.055</td>
<td>$t$ Change</td>
</tr>
</tbody>
</table>

Change Statistics

<table>
<thead>
<tr>
<th>$R^2$</th>
<th>$t$ Change</th>
<th>$df$</th>
<th>Sig. $F$ Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>.103</td>
<td>3</td>
<td>56</td>
<td>.109</td>
</tr>
<tr>
<td>.055</td>
<td>1</td>
<td>54</td>
<td>.001</td>
</tr>
</tbody>
</table>

a. Predictors: (Constant), Smoking, BMI, Age
b. Predictors: (Constant), Smoking, BMI, Age, SqEEPAEE
c. Dependent Variable: LnESR

coefficients

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Constant)</td>
<td>1.874</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>.617</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>.613</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>.273</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Constant)</td>
<td>3.616</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>.605</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>.617</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>.036</td>
</tr>
<tr>
<td></td>
<td>SqEEPAEE</td>
<td>.639</td>
</tr>
</tbody>
</table>

a. Dependent Variable: LnESR
Example of Statistics used in Chapter 9

Pearsons Correlation Coefficient: TEE and Sitting Time component

<table>
<thead>
<tr>
<th>Control Variables</th>
<th>SqRtSitting Correlation</th>
<th>TEE</th>
<th>Significance (2-tailed)</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.000</td>
<td>.030</td>
<td>0.896</td>
<td>19</td>
</tr>
</tbody>
</table>

Descriptives: SWA PAEE – IPAQ PAEE

<table>
<thead>
<tr>
<th>Difference (SWA - IPAQ)</th>
<th>Statistic</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.1783</td>
<td>.77362</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for Mean</td>
<td>-0.531</td>
<td></td>
</tr>
<tr>
<td>Upper Bound</td>
<td>3.0055</td>
<td></td>
</tr>
<tr>
<td>5% Trimmed Mean</td>
<td>1.0554</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>.9300</td>
<td></td>
</tr>
<tr>
<td>Variance</td>
<td>4.799</td>
<td></td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>2.19912</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>-1.47</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>5.98</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>7.45</td>
<td></td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>1.77</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
<td>1.613</td>
<td>.752</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>3.677</td>
<td>1.461</td>
</tr>
</tbody>
</table>

ICC: SWA PAEE and IPAQ PAEE

<table>
<thead>
<tr>
<th>Intraclass Correlation Coefficient</th>
<th>95% Confidence Interval</th>
<th>F Test with True Value 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraclass Correlation A</td>
<td>-.1900</td>
<td>-.173</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>1.570</td>
<td></td>
</tr>
<tr>
<td>F Test with True Value 0</td>
<td>df1-21</td>
<td></td>
</tr>
<tr>
<td>Average Measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraclass Correlation B</td>
<td>.331</td>
<td>1.570</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>21-21</td>
<td></td>
</tr>
</tbody>
</table>

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. Type A intraclass correlation coefficients using an absolute agreement definition.

b. The estimator is the same whether the interaction effect is present or not.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.