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Cardio-respiratory fitness, obesity and traditional cardiovascular disease risk factors in patients with rheumatoid arthritis

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Cardio-respiratory Fitness, Obesity and Traditional Cardiovascular Disease Risk Factors In Patients with Rheumatoid Arthritis

A thesis submitted to Bangor University for the degree of Doctor of Philosophy in the School of Sport, Health and Exercise Sciences

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Summary

Rheumatoid arthritis (RA) patients have an increased prevalence of cardiovascular disease (CVD). Traditional cardiovascular risk factors do not fully explain this increased incidence. Cardio-respiratory fitness and obesity are acknowledged CVD risk factors; however these are generally excluded when assessing CVD risk in RA patients. This PhD thesis aims to investigate the association between cardio-respiratory fitness and traditional CVD risk factors in RA patients and establish whether exercise can improve these CVD risk factors.

To determine cardio-respiratory fitness of RA patients a simple submaximal step test was validated (n=24). A cross sectional study was then carried out with 100 RA patients who underwent assessments of fitness (step test), RA disease, CVD risk factors and body composition. RA patient fitness level was poor (22 ± 6 ml·kg^{-1}·min^{-1}). Traditional CVD risk factors were not obviously elevated but poor fitness was strongly associated with poor body composition. Thirty-five patients were unable to complete the step test. These patients rated their arthritis as worse, more painful, disabling and had a greater prevalence of obesity. This study highlighted two important modifiable CVD risk factors (poor fitness and obesity) that are not routinely measured. An 8 week exercise intervention (n=10) designed to increase cardio-respiratory fitness was then implemented and improved cardiovascular health (systolic blood pressure), body composition (body fat, waist and hip circumference) and RA disease ($p < 0.05$).

RA patients are suffering from the effects of being unfit and overweight. Not only are they independent CVD risk factors, they impact considerably on patients disease perception and functional ability. These risk factors should be considered as part of RA care and information should be provided to help patients improve their cardiovascular health and general wellbeing. Regular exercise can help improve the above CVD risk factors as shown in this thesis.

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Cooney, J.K., Law, R.J., Matschke, V., Lemmey, A.B., Moore, J.P., Ahmad, Y., Jones, J.G., Maddison, P. and Thom, J. (2011). Benefits of exercise in rheumatoid arthritis. *Journal of Aging Research*, Volume 2011, Article ID 681640.

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Conference Presentations

The British Society for Rheumatology (BSR), April 12th – 14th 2011 – Poster Presentation. Validity and reliability of the Siconolfi Step Test for estimating cardio-respiratory fitness in rheumatoid arthritis patients. Jennifer K. Cooney, Dr. Jonathan Moore, Dr. Yasmeen Ahmad, Dr Andrew Lemmey, Dr. Jeremy Jones, Prof. Peter Maddison, Dr. Jeanette Thom.

The Society for Research in Rehabilitation (SRR), July 4th 2011 – Poster Presentation. Validity and reliability of the Siconolfi Step Test for estimating cardio-respiratory fitness in rheumatoid arthritis patients. Jennifer K. Cooney, Dr. Jonathan Moore, Dr. Yasmeen Ahmad, Dr Andrew Lemmey, Dr. Jeremy Jones, Prof. Peter Maddison, Dr. Jeanette Thom.

American College of Rheumatology (ACR), November 9th 2011 - Verbal Presentation. The association between cardio-respiratory fitness and traditional cardiovascular risk factors in rheumatoid arthritis (RA) patients. Jennifer K. Cooney, Dr. Jonathan Moore, Dr. Yasmeen Ahmad, Dr Andrew Lemmey, Dr. Jeremy Jones, Prof. Peter Maddison, Dr. Jeanette Thom.

The British Society for Rheumatology (BSR), May 1st – 3rd 2012 – Poster Presentation. Rheumatoid arthritis (RA) patients are too fat and unfit. Jennifer K. Cooney, Dr. Jeanette M. Thom, Dr. Jonathan P. Moore, Dr. Andrew B. Lemmey, Dr Jeremy G. Jones, Prof. Peter J. Maddison, Dr. Yasmeen A. Ahmad.

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Author's Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed ..... (candidate)
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STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated.
Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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Abbreviations

ABPI	Ankle Brachial Pressure Index
ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
AZA	Azathioprine
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	Cardiovascular Disease
CCP	Cyclic Citrullinated Peptide
CRP	C-Reactive Protein
DAS	Disease Activity Score
DBP	Diastolic Blood Pressure
DEXA	Dual X-ray Absorptiometry
DMARDs	Disease Modifying Anti Rheumatic Drug
ECG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
EULAR	The European League Against Rheumatism
Fc	Fragment Crystallizable
GP	General Practitioner
HAQ	Health Assessment Questionnaire
HDL-c	High Density Lipoprotein Cholesterol
HR	Heart Rate
HRM	Heart Rate Maximum
HSE	Health Survey for England
ICC	Intraclass Correlation Coefficient
IL-1	Interleukin - 1
IL-6	Interleukin – 6
IMT	Intima - Media Thickness
IPAQ	International Physical Activity Questionnaire
JBS	Joint British Society
LOA	Limits of Agreement
LDL-c	Low Density Lipoprotein Cholesterol
MAF	Multidimensional Assessment of Fatigue
MET	Metabolic Equivalent
MetS	Metabolic Syndrome
MTX	Methotrexate
NF- κβ	Nuclear Factor Kappa Beta
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NSAIDs	Non Steroidal Anti Inflammatory Drugs
OR	Odds Ratio
PRT	Progressive Resistance Training
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomised Control Trial
RER	Respiratory Exchange Ratio
RF	Rheumatoid Factor

ROM	Range of Motion
RPE	Ratings of Perceived Exhaustion
SBP	Systolic Blood Pressure
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
TC	Total Cholesterol
TG	Triglycerides
TNF-α	Tumor Necrosis Factor α
VAS	Visual Analogue Scale
$VO_{2\ max}$	Maximal Oxygen Uptake
WHO	World Health Organisation
Waist:Hip	Waist Hip Ratio

1 Chapter 1: Introduction

It is well documented that patients with rheumatoid arthritis (RA) have an increased risk of developing cardiovascular disease (CVD) (Avina-Zubieta et al., 2012, Wallberg-Jonsson et al., 1997). It is also believed that mortality from CVD is 50% higher in patients with RA when compared to the general population (Avina-Zubieta et al., 2008, Maradit-Kremers et al., 2005). However, the mechanisms underlying this increased risk of CVD in RA are not fully understood (Mutru et al., 1989, Symmons et al., 1998, Cavagna et al., 2012). Early research suggests that traditional CVD risk factors do not fully explain this increased incidence (Del Rincon et al., 2001, Solomon et al., 2003). The National Institutes of Health (NIH) define cardiovascular risk factors as conditions or habits that raise an individual's risk of developing heart disease (NIH, 2006). Hypertension, dyslipidemia, diabetes mellitus, smoking and obesity are very powerful predictors of CVD risk in the general population (Wilson et al., 1998). However, some studies suggest that the cardiovascular risk profile is no different in people with or without RA (Solomon et al., 2004). A study by del Rincon et al. (2005) suggested that established CVD risk factors needed to be present for systemic inflammation to promote atherosclerosis in RA (del Rincon et al., 2005).

As well as the traditional CVD risk factors listed above, poor cardio-respiratory fitness, defined as the body's ability to sustain physical activity, is an independent risk factor for CVD in the general population (Carnethon et al., 2003). RA patients have a significantly reduced cardio-respiratory fitness when compared to their age matched controls (Beals et al., 1985, Cimen et al., 2001, Ekdahl and Broman, 1992, Minor et al., 1988, Sokka and Hakkinen, 2008). However, despite evidence that RA patients have poor cardio-respiratory fitness and that poor fitness is a CVD risk factor in its own right, the measurement of cardio-respiratory fitness in clinical practice is generally nonexistent. This introduction will review the literature regarding cardio-respiratory fitness and CVD risk factors in RA and will aim to highlight the present deficiencies in the literature, which has led to the thesis' experimental studies.

1.1 Rheumatoid Arthritis

1.1.1 Rheumatoid Arthritis Definition and Classification

Arthritis (meaning inflammation of the joints) describes a group of conditions that cause joint damage. One of the most common inflammatory forms of arthritis is rheumatoid arthritis (RA) (Reginster, 2002). Given the presence of autoantibodies, such as rheumatoid factor (RF) and anti–citrullinated protein antibody (tested as anti–cyclic citrullinated peptide [anti-CCP]), RA is considered an autoimmune disease (Firestein, 2003). Autoimmunity and the overall systemic and articular inflammatory load drive the destructive progression of the disease. To date, the exact cause of RA remains unknown. However, various factors including genetic factors, environmental factors and infectious agents have been suggested as potential triggers of this disease (Feldmann et al., 1996). RA mainly affects the synovial joints, often in a symmetrical fashion and is characterised by pain, swelling and stiffness of the joints. RA is typically cyclical in nature, whereby an individual experiences periods of increased disease activity (known as flares) and periods of remission. The diagnosis of RA is based on a pattern of clinical and laboratory abnormalities. The American College of Rheumatology (ACR) outlined specific criteria for the classification of RA in 1987 (Arnett et al., 1988). The criteria for the classification of RA were formulated from a computerized analysis of 262 contemporary, consecutively studied patients with RA and 262 control subjects with rheumatic diseases other than RA (non-RA). The criteria were as follows:

1) Morning stiffness in and around joints lasting at least one hour before maximal improvement.
2) Soft tissue swelling of three or more joint areas observed by a physician.
3) Swelling of the proximal interphalangeal, metacarpophalangeal, or wrist joints.
4) Symmetric swelling.
5) Rheumatoid nodules as observed by a physician.
6) The presence of rheumatoid factor.
7) Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

A diagnosis of RA is made when at least four of the seven above criteria are present. The 1987 ACR criteria are the standard means of defining RA and are in widespread international use. However, more recently it has been suggested that this criteria is not without limitation.

It is believed that the 1987 ACR criteria fail to identify patients in the earlier stages of their disease. Because of this discrepancy, a new classification criterion has been developed; the 2010 ACR/EULAR criteria (Aletaha et al., 2010).

1.1.2 The Clinical Dilemmas in Rheumatoid Arthritis

RA is the most common form of chronic joint inflammation affecting 0.5-1% of the UK population (Symmons et al., 2002). It is most prevalent in individuals aged 40-60 years and the risk of developing RA is approximately 5 times higher in women (Panel, 2004). If left untreated, RA would lead to irreversible joint damage causing deformity and ultimately disability (Akil and Amos, 1995, Emery, 2002). As a consequence of their disease RA patients suffer severe joint pain, reduced mobility and reduced muscle strength (Akil and Amos, 1995, Ekdahl and Broman, 1992). Most RA patients also suffer from an accelerated loss of muscle mass; a condition known as "rheumatoid cachexia" (Roubenoff, 2008). This causes severe disability and has a significant impact on an individuals' quality of life. It has been suggested that less than half of patients with RA are still working after 10 years of disease (Sokka et al., 1999, Young et al., 2002). Thus, this disease has considerable social and economic consequences for both the individual and society (Reisine et al., 2007).

1.1.3 Treatment of Rheumatoid Arthritis

To date there is no known cure for RA. However, over the last decade the treatment of RA has changed dramatically (Grazio, 2008). Treatment of RA patients focuses on decreasing inflammation, limiting joint destruction, reducing pain and improving overall quality of life (QoL). This treatment comes in the form of medication, surgery and rehabilitation. The most common medications used are listed in Table 1.1 (Gaffo et al., 2006).

Table 1.1 Summary of the main drug treatment in RA

TYPE	MEDICATION	AIM
NSAID	Diclofenac Naproxen Ibuprofen	Reduce pain & inflammation
Steroid	Prednisone	Reduce pain & inflammation Slow disease progression Decrease joint damage
DMARD	Methotrexate Sulphsalazine, Hydroxychloroquine Leflunomide	Reduce pain & inflammation Slow disease progression Decrease joint damage
Biologic	Infliximab Etanercept Adalimumab Tociluzimab Rituximab	Decrease TNF Decrease B-cell Decrease IL-6 Slow disease progression Decrease joint damage

NSAID; Non steroidal anti inflammatory drug, DMARD; Disease modifying anti rheumatic drug, TNF; Tumor necrosis factor, IL-6; Interleukin-6.

1.2 Extra-articular Disease Manifestations

Although RA is primarily a 'joint' disease, the systemic nature of RA means that it is also associated with a number of extra-articular organ manifestations. The prevalence of systemic manifestations in RA is approximately 8-12%; however this figure does not include cardiovascular disease (CVD) (Turesson and Jacobsson, 2004, Turesson et al., 2002). These extra-articular manifestations are strongly associated with increased disease activity and with markers of inflammation, such as higher levels of C-reactive protein (CRP) (Baecklund et al., 2006, Hannawi et al., 2007, Van Doornum et al., 2002). The most common extra-articular manifestations include rheumatoid nodules, cardiopulmonary disease (pleural effusion, nodules, and interstitial lung disease), Sjogrens syndrome (dry eyes and mouth), rheumatoid vasculitis, peripheral neuropathy, rheumatoid cachexia and cardiovascular disease (Turesson et al., 2003). For the purpose of this thesis only cardiovascular disease will be discussed in more detail.

1.2.1 Cardiovascular Disease (CVD)

The World Health Organisation (WHO) defines CVD as a general term used to describe conditions that affect the heart and blood vessels. These include atherosclerosis, coronary heart disease (angina, myocardial infarction), stroke, heart failure and peripheral arterial disease. Statistics from the British Heart Foundation (BHF) show that CVD causes one in three deaths in the general UK population, making it the most common cause of death in the UK (BHF, 2009). The development of CVD is strongly associated with CVD risk factors. A risk factor is simply a condition or habit that increases an individual's risk of developing CVD. These risk factors can be modifiable (e.g. hypertension) or non modifiable (Pyorala et al., 1994).

1.2.1.1 Modifiable CVD Risk Factors

Modifiable CVD risk factors include:

1) Hypertension: defined as a blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic or receiving antihypertensive medication. Hypertension is the strongest risk factor for stroke and plays a significant role in the development of heart attacks. The positive association between systolic blood pressure or diastolic blood pressure and risk of developing CVD disease is well established (Frohlich, 1997).
2) Dyslipidemia: defined as high total cholesterol (> 5.2 $mmol \cdot l^{-1}$), high triglycerides (> 1.8 $mmol \cdot l^{-1}$), high low density lipoprotein cholesterol (LDL-c) (> 3.4 $mmol \cdot l^{-1}$) or on lipid lowering therapy. Elevated lipid levels in serum are associated with an increased risk in the development of CVD (Cullen, 2000).
3) Smoking: cigarette smoking substantially increases an individual's CVD risk. Current cigarette smokers have a 70% increased risk of fatal coronary heart disease (CHD). The overall incidence of nonfatal CHD as well as sudden death is two to fourfold higher in cigarette smokers (Jonas et al., 1992, Willett et al., 1987).
4) Diabetes mellitus: defined as a high fasting glucose (> 7.0 $mmol \cdot l^{-1}$) or receiving treatment for diabetes. Diabetes mellitus increases the risk of developing CHD by three to sevenfold in women and by two to threefold in men (Grundy et al., 1999).

5) Obesity: defined as a high body mass index (BMI) (> 30 $kg.m^{-2}$). Over the last 20 years the prevalence of obesity has escalated worldwide (Engeland et al., 2003) and is strongly associated with an increased risk of developing CVD (Poirier and Eckel, 2002). This is discussed in further detail in section 1.3.2.
6) Physical Inactivity: being physically inactive/unfit has been shown to significantly increase the risk of developing CHD (Hasselstrom et al., 2002, LaMonte et al., 2000). However, when determining the CVD risk of an individual, the assessment of their cardio-respiratory fitness is often ignored. This is discussed in further detail in section 1.4.

1.2.1.2 Non Modifiable CVD risk factors

It is accepted that modifiable CVD risk factors can be improved either by a change in lifestyle or by medication. However, there are some other risk factors which an individual cannot change. These are known as non-modifiable risk factors and they include:

1) Age: over the age of 55 years, the risk of developing CVD increases significantly (Smith et al., 2004).
2) Gender: males have a greater CVD risk when compared to pre-menopausal females. However, after the menopause a females risk is believed to be similar to that of males (Mercuro et al., 2010).
3) Family history: a person is considered to have a family history of heart disease if they have a first-degree blood relative that has had CHD or stroke before the age of 55 years (for a male relative) or 65 years (for a female relative) (Assimes, 2010, Bachmann et al., 2010).
4) Ethnicity: individuals from African or Asian descent have a higher risk of developing CVD than other racial groups (Chaturvedi, 2003).

CVD is partially attributed to traditional CVD risk factors and global CVD risk can be estimated using a number of risk stratification algorithms. One of the most widely used CVD risk scores is the Framingham risk score (Eichler et al., 2007). The Framingham risk score was originally developed for use in the North American population and has since been shown to be less accurate when used in other populations, e.g. the UK (Brindle et al., 2003). Because of this, other CVD risk scores have been developed. These include the QRISK2 and the Joint

British Society (JBS) risk scores (Crowson et al., 2012). These are explained in further detail in Chapter 2.

Another method for assessing the CVD risk of an individual is the clustering of CVD risk factors. This concept originally described as 'Syndrome X' is now known as Metabolic Syndrome (MetS) (Kahn, 2008). MetS is a cluster of 3 or more of the following abnormalities: increased waist circumference, elevated triglycerides, reduced high density lipoprotein, elevated blood pressure and elevated fasting glucose. It is considered a significant and independent risk factor for CVD (Galassi et al., 2006). Fulfilment of the criteria for MetS is thought to increase CVD risk by two to threefold (Bray and Bellanger, 2006).

1.3 Rheumatoid Arthritis and Cardiovascular Disease (CVD)

1.3.1 Cardiovascular Disease Risk in Rheumatoid Arthritis

It has already been established that CVD is an extra-articular feature of RA disease. RA is associated with increased morbidity and mortality from atherosclerosis (Bacon and Townend, 2001). It is believed that up to 50% of deaths in RA patients are attributable to CVD, whilst cerebrovascular disease accounts for the second greatest cause of excess mortality in RA patients (Wolfe et al., 1994). Thus the majority of the CVD observed in this population may result from premature atherosclerosis (Salmon and Roman, 2008). It has been reported that the average lifespan of an RA patient is shortened by 3 – 18 years (Van Doornum et al., 2002) and that the CVD risk of an RA patient is equivalent to the CVD risk of someone without RA who is 10 years older (Kremers et al., 2008). The exact cause for this increased incidence of CVD in RA remains unclear.

Research to date has focused on fatal cardiovascular events in RA (Kremers et al., 2005, Nurmohamed, 2009, Solomon et al., 2003) and traditional risk factors often using CVD risk stratification algorithms like the Framingham risk score (Chung et al., 2006, Dessein et al., 2005). However, some researchers believe that traditional risk factors of CVD like smoking, obesity, diabetes mellitus and physical inactivity do not fully explain the increased incidence of CVD in the RA population. An early investigation suggested that RA patients had a higher

rate of cardiovascular events compared to healthy people even after adjustments for traditional risk factors (Del Rincon et al., 2001). Their observations have subsequently led other researchers to believe that additional mechanisms other than traditional risk factors are responsible for the significant cardiovascular risk in RA patients. It has been hypothesised that inflammation may be a primary contributor to CVD in RA (Kremers et al., 2005) with other traditional risk factors such as smoking, hypertension, obesity, and diabetes mellitus having a less significant role than that observed in the general population (Gonzalez et al., 2008, Quyyumi, 2006).

RA is characterised by severe inflammation of the synovium where there is a 3-100 times elevation of pro inflammatory cytokines (interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) and markers of inflammation (e.g. CRP) (Feldmann et al., 2001). It has been suggested that these circulating cytokines may play a significant role in vascular disease (Sattar et al., 2003) by promoting the development of premature atherosclerosis. The exact cause of this increased atherosclerosis in RA is unclear but studies investigating the effects of inflammation on the promotion of atherogenesis suggest that IL-6 and TNF-α are particularly important in this process (Rho et al., 2009). This notion is supported by the observations that anti-TNF-α agents improve endothelial dysfunction (Hurlimann et al., 2002) and reduce carotid intima-media thickness (Del Porto et al., 2007). These observations suggest that specific inflammatory markers promote endothelial dysfunction, the first step in the pathogenesis of atherosclerosis (Yasmin et al., 2004), see Figure 1.1.

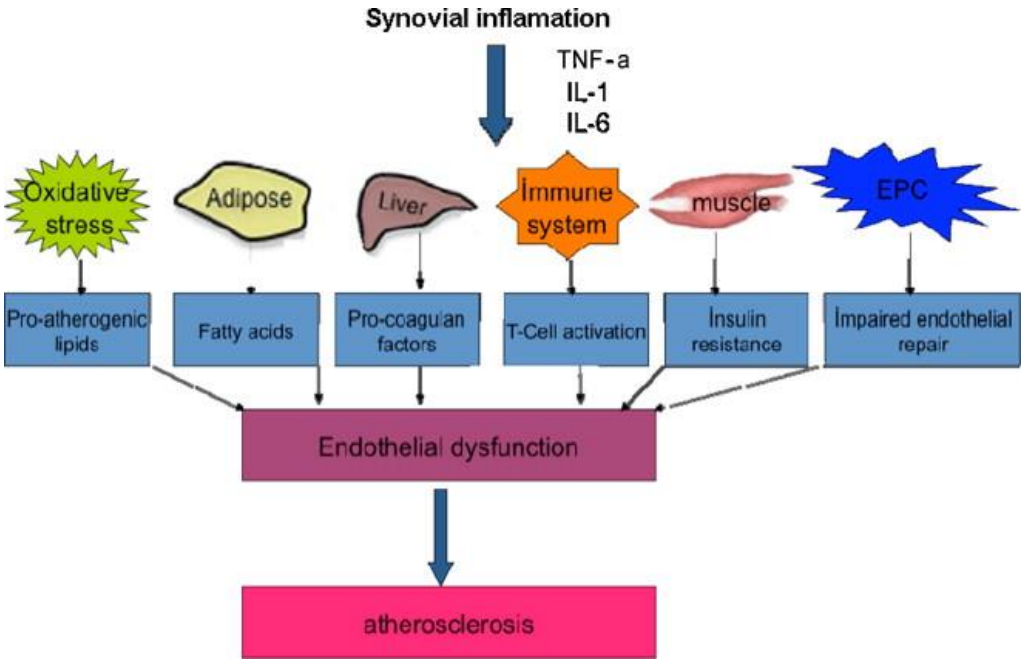

Figure 1.1 Inflammatory pathways linked to the development of atherosclerosis in patients with rheumatoid arthritis (Ozbalkan et al., 2010). EPC; endothelial progenitor cells.

Since RA is a chronic inflammatory disorder, the control of inflammation with medication is essential. However, some medications like corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) may also cause hypertension, insulin resistance and dyslipidemia (Johnson, 1997, Kalback, 1972, Quyyumi, 2006). A recent meta-analysis suggested that NSAIDs like naproxen, diclofenac and ibuprofen are not well tolerated in terms of cardiovascular risk (Trelle et al., 2011). Suggestions have been made that prolonged administration of NSAIDs have been shown to increase the risk of non fatal myocardial infarction (García Rodríguez and Gozalez-Perez, 2005). However, not all medications used in the treatment of RA have adverse effects on CVD risk. Disease modifying anti rheumatic drugs (DMARDs) like methotrexate have been shown to reduce CVD risk (Westlake et al., 2010).

Despite earlier research suggesting that traditional CVD risk factors do not explain the increased incidence of CVD in RA, many studies continue to investigate the potential role of traditional risk factors in the development of CVD in RA. However, their findings are somewhat conflicting. Some studies suggest that RA patients have a higher systolic blood pressure (Alkaabi et al., 2003), dyslipidemia (Metsios et al., 2009), increased incidence of diabetes, and greater BMI (Del Rincon et al., 2001) than those without RA. While other

studies have reported the opposite and found that the prevalence of hypertension in RA is no different to that of the general population (Boyer et al., 2011) and that dyslipidemia actually has a paradoxical effect on CVD risk in patients with RA, with lower lipid levels resulting in a greater CVD risk (Semb et al., 2010). As in the general population, CVD risk scores have been used to estimate CVD risk in RA patients; Chung et al. (2006) investigated the Framingham risk score of a group of RA patients and healthy matched controls. RA patients with long standing RA had a significantly higher Framingham CVD risk score when compared to healthy controls (Chung et al., 2006). However, despite its widespread use the Framingham risk score often underestimates risk in certain populations, especially women (Mahoney et al., 2001). Since women are most commonly affected by RA, and the knowledge that traditional risk factors often behave differently in RA, the Framingham risk score may not be such an accurate estimation of CVD risk in this population. It has even been suggested that risk scores like the Framingham underestimate CVD risk by fivefold in some RA patients. Other studies have investigated the prevalence of the MetS to estimate the CVD risk of RA patients. However, their results have also been somewhat questionable due to the differences in the definitions used to classify MetS (Pereira et al., 2009). Some studies show that RA patients have a higher prevalence of MetS compared to individuals without RA (Chung et al., 2008, Crowson et al., 2011) and that those patients with long standing RA have an even greater prevalence of MetS compared to patients with early RA (Chung et al., 2008).

It is evident from the literature that RA related systemic inflammation contributes to the accelerated atherogenesis observed in RA, even when other traditional risk factors are taken into consideration (Ozbalkan et al., 2010). However, with modern drug treatment, tight control of RA is possible; in fact, CVD event rates are reported to be lower in patients treated with methotrexate (Micha et al., 2011). Despite these advances in medical treatment, the rate of CVD morbidity and mortality still remain high when compared to the general population. The European League against Rheumatism (EULAR) has highlighted the need for RA specific methods to identify patients with a high CVD risk (Peters et al., 2010). Two independent CVD risk factors that have been mentioned previously in this current chapter but have not received much attention in the study of RA patients are obesity and cardio-respiratory fitness. The impact of obesity and poor cardio-respiratory fitness in relation to CVD risk factors in patients with RA is unknown.

1.3.2 Obesity

Obesity is a well established risk factor for the development of CVD (Sowers, 2003). It is the excessive accumulation of body fat that fundamentally occurs from an energy imbalance between calories consumed and calories expended (Bray and Bellanger, 2006). The World Health Organisation (WHO) defines obesity as a body mass index (BMI) (weight divided by height squared) of greater than 30 $kg \cdot m^{-2}$. A BMI of 25 – 30 $kg \cdot m^{-2}$ represents the overweight category. Data from the Health Survey for England (HSE) showed that in 2009, 61% of adults (aged 16 or over) in England were overweight or obese, of these 23% were obese (i.e. 1 in 4 adults in England are obese). This is similar to statistics reported by the Welsh Health Survey (2010) - 3 in 5 adults were classified as overweight or obese, with 1 in 5 adults classified as obese. This level of obesity is a significant burden on the National Health Service (NHS). Direct costs caused by obesity are estimated to be £4.2 billion per year and forecast to more than double by 2050 if this trend continues (Weiler and Stamatakis, 2010).

Obesity has a severe impact on an individual's health. It is an independent risk factor of many chronic diseases such as diabetes mellitus, CVD and some cancers; endometrial, breast and colon cancer (Bergstrom et al., 2001). WHO reported that being overweight and obesity are the fifth leading risks for global death (WHO, 2009). It is suggested that individuals who are overweight or obese have a decreased life expectancy of 3 - 7 years (Peeters et al., 2003). Adults who are overweight or obese have elevated serum levels of C-reactive protein, IL-6, TNF-α, and leptin, which are all known markers of inflammation (Das, 2001). This suggests that obesity may be a low-grade systemic inflammatory disease (Bullo et al., 2003). Not only is obesity a problem in the general population, it is also a significant problem in patients with RA and is likely a result of genetic and lifestyle influences (Marti et al., 2004).

1.3.3 Obesity in RA

RA is a chronic inflammatory disease that is associated with altered body composition (Giles et al., 2008). The chronic inflammation of the disease, particularly activation of the nuclear factor kappa-beta (NF- κβ) pathway, triggers metabolic alterations leading to the degradation of lean tissue, especially muscle mass (Marcora et al., 2006). If this is combined with an inactive lifestyle, a reduction in muscle mass with an increased accumulation of fat mass may

result. This process is well known as rheumatoid cachexia (Roubenoff et al., 1994). It is believed that approximately two thirds of RA patients suffer from rheumatoid cachexia (Elkan et al., 2009, Walsmith et al., 2004). Not only do these detrimental alterations in body composition cause increased muscle weakness and disability; it can also contribute to feelings of fatigue and increased risk of CVD (Metsios et al., 2009, Roubenoff et al., 1994).

Despite the fact that obesity is an independent risk factor for CVD in the general population and that RA patients have an increased risk of CVD, very few studies have directed their focus on obesity in the RA population. Most RA patients have their weight routinely assessed when they attend rheumatology clinics. However, this is mainly used as a demographic characteristic reported in medical notes and is generally excluded from further interpretation (Stavropoulos-Kalinoglou et al., 2011).

The WHO definition for obesity using BMI is valid for the general population. However, it has been proven inaccurate for some populations with altered body composition (Evans et al., 2006, Goh et al., 2004). As patients with RA can often have increased fat mass with little or no change in total body weight, the standard BMI cut off value may not be useful in RA patients. Stavropoulos-Kalinoglou et al. (2007) compared the BMI of patients with RA to that of the general population. For a given body fat content measured by bioelectrical impedance analysis patients with RA had a significantly lower BMI by almost 2 $kg.m^{-2}$. Consequently it is proposed that the BMI cut offs for RA patients should be reduced to 23 and 28 $kg.m^{-2}$ to define overweight and obesity respectively (Stavropoulos-Kalinoglou et al., 2007). A recent review of the literature on obesity in RA reported that the BMI of RA patients ranged from 26.5 – 28.2 $kg.m^{-2}$ which is similar to that of the general population (Stavropoulos-Kalinoglou et al., 2011). A UK based study found that 68% of RA patients were overweight (BMI > 25 $kg.m^{-2}$) and 31% were obese (BMI > 30 $kg.m^{-2}$) (Armstrong et al., 2006). These values are marginally higher than that reported by the HSE in 2009 for the general population – 61% and 23% for overweight and obese, respectively. However, if RA specific cutoffs were used then an even higher prevalence of obesity (37%) would be observed (Stavropoulos-Kalinoglou et al., 2007).

It is clear from the literature to date that more research is needed to identify the optimal method for assessing obesity in RA patients. Although the suggestions made by Stavropoulos-Kalinoglou et al. (2007) to lower BMI cut offs seem promising, further research

is needed on the validity of these revised criteria. Perhaps the best solution is to examine several measures of body composition to determine obesity.

1.3.4 Measures of Obesity

The assessment of body composition is quite challenging as direct measurement of adipose tissue *in vivo* is virtually impossible. Because of this several alternative indirect and easy to use methods have been developed. The main tests of body composition are discussed below.

1.3.4.1 Body Mass Index (BMI)

BMI is the most common method of measuring obesity (Burkhauser and Cawley, 2008). However, it may not be the most suitable measure of obesity in RA patients (Stavropoulos-Kalinoglou et al., 2007) (see section 1.3.3). BMI is an index that assesses obesity on a whole body level; it takes into account total weight but it does not distinguish between the different tissues that make up the human body. Total body weight = fat mass + lean mass (muscle, organs, bone). Thus, individuals of similar height and weight can have significantly different levels of lean mass. Their BMI would be equal but body fat could differ significantly. This is one of the major limitations of using BMI as a measure of obesity.

1.3.4.2 Waist Circumference and Waist Hip Ratio (Waist:Hip)

Waist circumference is an indirect measure of central adiposity (Lean et al., 1995). In adults central adiposity is known to be associated with increased risk of obesity-related conditions including type 2 diabetes, hypertension and heart disease (Seidell, 2010). Although indices of central adiposity are closely correlated with BMI, they have been shown to predict future ill health independently of BMI (Yusuf et al., 2005). The WHO (WHO, 2008) has advised that an individual's relative risk of obesity-related ill health can be more accurately classified using both BMI and waist circumference than by either alone (Huxley et al., 2010). The WHO has developed a set of thresholds to categorise an individual's risk of obesity-related illness based on waist circumference. For European men and women the cut-off points for waist circumference are 94 cm and 80 cm, respectively. However, NICE guidelines state that if waist circumference exceeds 102 cm for men and 88 cm for women, there is an even greater risk of ill health (NICE, 2006). Abdominal obesity is further defined by waist hip

ratio (Waist:Hip). A Waist:Hip above 0.90 for males and above 0.85 for females indicates a substantially increased risk of metabolic complications (WHO, 1995).

1.3.4.3 Body Fat Percentage

A proportion of body fat is vital for normal physiological functioning; this is referred to as essential fat. For men essential fat is approximately 2-5% and naturally higher for women at 10-13% (Gallagher et al., 2000). The rest of the total body fat is called storage fat, this is the excess fat stored in adipose tissue. Storage fat can accumulate around internal organs (visceral fat) or under the skin (subcutaneous fat). Optimal levels of body fat for females and males are outlined below in Figure 1. 2.

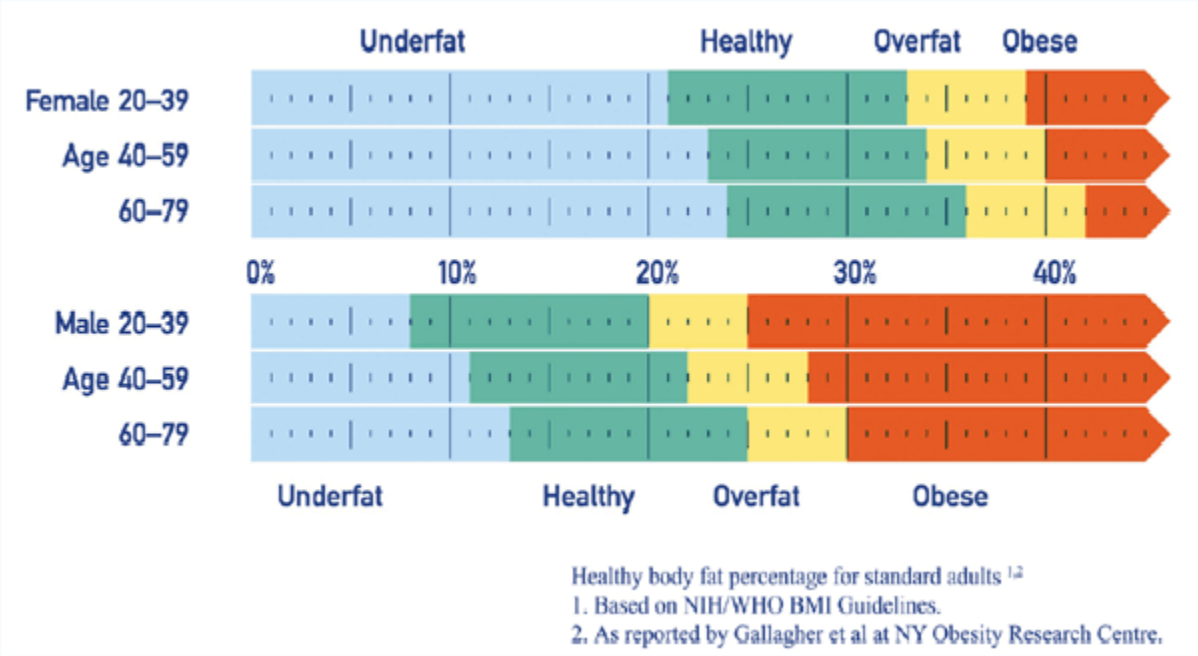

Figure 1.2 Percent body fat norms based on NIH and WHO guidelines (WHO, 2000).

Body fat percentage can be assessed using several methods including skinfold thickness, bioelectrical impedance analysis (BIA), hydrostatic weighing and dual x-ray absorptiometry (DEXA). Below is a brief description of each method.

Skinfold Thickness

This method simply involves the measurement of skinfolds of the body at various sites. The 4 spot formula is considered to be relatively accurate (Durnin and Womersley, 1974). This method determines body fat based on the sum of 4 skinfolds (biceps, triceps, subscapular and

iliac crest). Although this method is quick and requires minimal equipment, the accuracy of this technique is observer dependent.

Bioelectrical Impedance Analysis (BIA)

BIA is relatively simple, quick and a non-invasive measure of body composition with minimal intra- and inter-observer variability (Diaz et al., 1989). The benefit of BIA is that results are available immediately and reproducible with < 1% error on repeated measurement (Segal et al., 1991). This technique became commercially available for the first time in the mid-1980s (Buchholz et al., 2004), and requires inexpensive, portable equipment, making it an appealing alternative to assess body composition in epidemiological studies.

Hydrostatic weighing

Hydrostatic or underwater weighing is based on Archimedes Principle of displacement which states that the buoyant force on a submerged object is equal to the weight of the fluid that is displaced by the object. Until recently this method of assessing body composition was considered to be the gold standard. Hydrostatic weighing involves the measurement of body weight in and out of the water. After the correction for residual volume, percent fat can be calculated based on the underwater weight using standard equations (Brozek et al., 1963).

Dual x- ray absorptiometry (DEXA)

Whilst the above techniques assume two body compartments, DEXA can estimate three body compartments consisting of fat mass, lean body mass, and bone mass. DEXA systems use a source that generates X-rays at two energies. The differential attenuation of the two energies is used to estimate the bone mineral content and the soft tissue composition. When two X-ray energies are used, only two tissue compartments can be measured; therefore, soft tissue measurements (i.e., fat and lean body mass) can only be measured in areas where no bone is present. DEXA measurements are based in part on the assumption that the hydration of fat-free mass remains constant at 73%. Hydration, however, can vary from 67%–85%. DEXA is considered by many to be the new reference method (Van Der Ploeg et al., 2003). Despite this, a long assessment time and exposure to radiation makes this method unsuitable for use in large studies.

1.4 Cardio-respiratory Fitness

Another acknowledged independent risk factor for CVD is reduced cardio-respiratory fitness (Blair et al., 1989, Carnethon et al., 2003, Sandvik et al., 1993). Cardio-respiratory fitness is a measure of the body's ability to uptake, transport and utilize oxygen during sustained physical activity (ACSM, 2000, Hartung et al., 1993). The criterion measure of cardio-respiratory fitness is maximal oxygen uptake ($VO_{2\ max}$) (Armstrong et al., 1991). Cardio-respiratory fitness is typically expressed in litres of O_2 consumed per minute or in millilitres of O_2 consumed per kilogram of body mass per minute. Factors influencing cardio-respiratory fitness include non-modifiable factors like gender, age and genotype (Buskirk and Hodgson, 1987) and modifiable factors such as physical activity, obesity and medical condition (Lee et al., 2010). Typically males have a $VO_{2\ max}$ 40-60% higher than females (McArdle et al., 2005). This difference is most notably due to the variance in muscle mass and stroke volume between males and females (Fletcher et al., 2001). Age is also a major influencing factor; maximal oxygen intake declines by approximately 5 $ml \cdot kg^{-1} \cdot min^{-1}$ per decade from 25 to 65 years of age, with some possible acceleration thereafter (Shephard, 1987, Weiss et al., 2006). Potential causes of this age-related loss in cardio-respiratory fitness include decreases in maximal heart rate, stroke volume and arterio-venous oxygen difference (Weiss et al., 2006). Refer to Tables 1 and 2 in Appendix 1 for normative fitness data between gender and age groups taken from Heywood (1998).

Cardio-respiratory fitness is a sensitive and reliable measure of habitual physical activity (ACSM, 1998, Church et al., 2007), but it is also a very useful health indicator for both symptomatic and asymptomatic patients in clinical practice (Myers et al., 2002). An association between cardio-respiratory fitness and all cause mortality was first identified by Blair and colleagues (Blair et al., 1989). Data from numerous subsequent epidemiological studies indicate that low cardio-respiratory fitness is a strong independent risk factor for all-cause and cardiovascular disease (CVD) mortality in asymptomatic individuals, persons with co-morbid conditions (hypertension, obesity, type 2 diabetes mellitus), and those with established coronary artery disease (Franklin and McCullough, 2009). It is reported that the strength of association between low cardio-respiratory fitness and mortality is comparable to that between mortality and traditional CVD risk factors such as obesity, hypertension, dyslipidemia and smoking (Blair et al., 1989, Laukkanen et al., 2004, Wei et al., 1999). It has also been suggested that the measure of cardio-respiratory fitness ($VO_{2\ max}$) is the only

variable other than age and co-morbidity to be predictive of future dependence in the elderly (Paterson et al., 2004).

Despite the convincing evidence that fitness is associated with morbidity and mortality independently of other CVD risk factors (Carnethon et al., 2003, Kodama et al., 2009), the importance of cardio-respiratory fitness is still often overlooked from a clinical perspective compared with other more 'traditional' risk factors like high blood pressure, abnormal lipids, or smoking (Lee et al., 2010). The same is true for patients with RA.

1.5 Cardio-respiratory Fitness in RA

Research has shown that patients with RA have poor cardio-respiratory fitness in comparison to healthy age matched controls with some studies reporting a cardio-respiratory fitness level 20-30% lower in comparison to individuals without RA (Cimen et al., 2001, Ekdahl and Broman, 1992). This discrepancy in cardio-respiratory fitness level may be due to physical inactivity during inflammatory stages of the disease and continued physical inactivity during stages of disease remission (Mancuso et al., 2007).

Taking into consideration the established association between cardio-respiratory fitness and CVD risk, it seems reasonable to believe that the poor cardio-respiratory observed in RA patients may exacerbate, or even contribute to, some individuals heightened CVD risk. However, this potential link has not been tested.

1.6 Measures of Cardio-respiratory Fitness

There are two ways cardio-respiratory fitness can be measured, directly using a maximal exercise test or indirectly using a submaximal exercise test. The gold standard for assessing cardio-respiratory fitness is a $VO_{2\ max}$ test (Shephard et al., 1968); this is a maximal exercise test which is typically performed using a treadmill or a cycle ergometer. Although this is the more accurate measure of cardio-respiratory fitness this test is not without limitations. A $VO_{2\ max}$ test requires expensive equipment, trained personnel, maximal effort from the participant and an element of risk when performing such a test. Major complications like myocardial

infarction or serious arrhythmias can occur and have been reported at a rate of up to 5 per 10,000 tests, with sudden cardiac death occurring in up to 0.5 per 10,000 tests (Arena et al., 2007). Maximal exercise testing in clinical patients can often be limited by cardiopulmonary, musculoskeletal, and neuromuscular impairments and complaints such as exertion, dyspnea, fatigue, weakness, and pain (Noonan and Dean, 2000). Due to these limitations submaximal exercise tests are often used to predict cardio-respiratory fitness.

Submaximal exercise tests estimate cardio-respiratory fitness from exercise heart rate, oxygen consumption or exercise time to exhaustion. This estimation is based on the linear relationship between exercise heart rate and oxygen consumption (VO_2) (Astrand and Ryhming, 1954). Typically submaximal exercise tests are less difficult to perform, less time consuming and more importantly provide an adequate estimate of cardio-respiratory fitness. A review by Noonan and Dean (2000) reported a high correlation between maximal and submaximal exercise testing ($r = 0.7–0.9$) in various submaximal tests such as submaximal treadmill and cycle ergometer tests, 12-minute run test, and 1-mile walk test (Noonan and Dean, 2000).

To date, various submaximal exercise tests have been developed. These include tests designed to meet the needs of people with various functional limitations and disabilities and the needs of older adults (Brown et al., 1985, Bruce et al., 1973, Hagberg, 1994, Marciniuk and Gallagher, 1994). Bruce et al. (1973) developed the Modified Bruce Treadmill Test which is widely used to estimate $VO_{2\ max}$ especially in individuals with coronary heart disease (Bruce et al., 1973). Astrand and Rhyming (1954) developed a submaximal cycle ergometer test (A-R cycle ergometer test) which is based on the linear relationship between oxygen consumption and heart rate. It is one of the most widely used cycle ergometer tests that is often used to assess fitness and develop training programmes (Astrand and Ryhming, 1954). However, some studies using this test have reported that the protocol can elicit lower-extremity discomfort in some people, which may invalidate the results (Wisen and Wohlfart, 1995). Other submaximal exercise tests include the single stage treadmill walking test (Ebbeling et al., 1991). This walking test is reported to be suitable for individuals of all ages and fitness levels and in particular for those who suffer from fatigue. The above submaximal exercise tests have been previously validated in healthy populations and some clinical

populations. The walking test has also been validated in individuals with rheumatic disease (Minor and Johnson, 1996).

Despite various submaximal exercise tests being valid and reliable predictors of cardio-respiratory fitness in healthy individuals and various other clinical populations it is not unreasonable to suggest that these tests are not suitable for use in a clinical setting. The equipment needed (motorised treadmills or cycle ergometers) to perform these tests are expensive and require a lot of space. Some of the tests are even time consuming and often require trained personnel. In contrast, step tests that require limited equipment (i.e. step, metronome, heart rate monitor and stop watch), represent an attractive modality for assessing cardio-respiratory fitness in a clinical setting. Since the earliest reported step test, now known as the Harvard step test (Brouha et al., 1943), numerous submaximal step test protocols have been developed. These include the Queens College step test (McArdle et al., 1972), the Canadian home fitness test (Shephard, 1976), the Chester step test (Sykes and Roberts, 2004) and the Siconolfi step test (Siconolfi et al., 1985). Siconolfi et al. (1985) developed a simple step test to predict cardio-respiratory fitness in a healthy population. It was shown to be a valid predictor of directly measured $VO_{2\ max}$ ($r = 0.92$) and very reproducible. An advantage of the Siconolfi test over the others is that it may be completed at relatively low levels of exercise. This is very important in low active, clinical groups like patients with RA where exercise intolerance is a feature of their disease. The benefits of this step test are that it requires minimal time, effort, space and equipment, which is ideal for use in a clinical setting. Because of this, Marcora and colleagues used this step test with a group of systemic lupus erythematosus (SLE) patients and found it to be a valid and reliable measure of cardio-respiratory fitness in this clinical population (Marcora et al., 2007). As predictive exercise tests are population specific this test would need to be validated in a group of RA patients before it could be used in a clinical setting as a measure of cardio-respiratory fitness. This is discussed in further detail in Chapter 3.

1.7 Exercise and Rheumatoid Arthritis

In addition to the drug treatment described in section 1.1.3, there is growing scientific evidence that exercise is both safe and very beneficial for RA patients (Bearne et al., 2002, de Jong and Vliet Vlieland, 2005, Minor, 1996, Minor et al., 1989, Munneke et al., 2005).

Unfortunately, research has also shown that RA patients often fear disease aggravation and the traditional approach of rheumatology health professionals to recommend exercise restriction may explain the inactive lifestyle of this population (de Jong et al., 2003, Scott and Wolman, 1992). However, recently it has been well documented that properly designed physical exercise programmes can have very beneficial effects on cardio-respiratory fitness, strength and physical functioning without increasing disease activity or joint damage (Hakkinen, 2004, Westby, 2001).

An early meta-analysis of six randomised controlled trials suggested that dynamic exercise therapy was effective in improving aerobic capacity, muscle strength and joint mobility without any deleterious effects on disease activity (Van den Ende et al., 1998). Subsequently a large number of studies that have been subject to systematic review (Baillet et al., 2010, Hurkmans et al., 2009, Roubenoff et al., 1992, Stenstrom and Minor, 2003) indicate that exercise is effective in the management of patients with RA, and does not induce adverse effects. In fact exercise has been shown to improve functional ability (de Jong et al., 2003) and significantly reduce pain (Van den Ende et al., 2000).

Whilst the exercise benefits for RA patients are widely recognized and suggested to be beneficial for most RA patients (NICE, 2009). The conclusion of many exercise programmes is that more research is required to investigate the most effective exercise prescription (intensity, frequency, duration, and mode), the optimum modes of exercise delivery, and how adherence to training can be facilitated. A summary of exercise types and recommendations for individuals with RA based on current evidence is depicted in Table 1.2 (Cooney et al., 2011).

Table 1.2 Summary of general exercise guidelines for RA. This information is derived from ACSM exercise management guidelines (Durstine et al., 2003) and the research literature (Cooney et al., 2011).

Benefit	Type of Exercise	How Best to Achieve
Improve CV health	Cycling Walking Swimming Dance	60–80% HR max 30–60 mins/session 3–5 days/week Increase duration, then intensity over time
Increase muscle mass & strength	Free weights Weight machines Therabands	60–80% 1RM 8–10 exercises (large muscle groups) 8–12 reps/exercise 2-3 sets 2-3 days/week Increase intensity over time
Increase ROM & flexibility for enhanced joint health	Stretching Tai Chi exercises Yoga/Pilates	10–15 minutes 2 days/week
Improve balance*	One leg stance Stability ball Strengthening core muscles	On a regular basis

*The effects of balance training alone in RA patients to enhance functional capacity through increased proprioception and coordination and to reduce the risk of falls have yet to be conducted (Silva et al., 2010). Thus the effectiveness and safety of balance training are unclear. HR; heart rate, RM; repetition maximum, ROM; range of motion.

Typically exercise interventions in RA have focused on the effects of aerobic training, progressive resistance training (PRT) and a combination of both types. Aerobic activities most often included in exercise interventions are walking, running, cycling, exercise in water, and aerobic dance. Walking is a good mode of exercise as it is inexpensive, requires no special skills, is safe, and can be performed both indoors and outdoors. Regular brisk

walking, even in short bouts, improves aerobic fitness and reduces aspects of CVD risk in healthy adults (Forestier et al., 2009). Cycling is also an excellent mode of aerobic activity that works the large muscle groups of the lower extremity. Cycling, in line with the guidelines in Table 1.2, improves aerobic capacity, muscle strength, and joint mobility with no exacerbation of disease activity (Van den Ende et al., 1996). Water-based exercise has also been studied in RA. Hydrotherapy has been shown to be very effective for RA sufferers. As little as two 30-minute sessions for 4 weeks have been shown to significantly reduce joint tenderness, improve knee range of movement, and improve emotional and psychological well-being (Hall et al., 1996). Dancing is another form of aerobic exercise which has reported improvements in aerobic power and resulted in positive changes in depression, anxiety, and fatigue, with no deterioration in disease activity in RA patients (Noreau et al., 1995). However, despite the large number of studies demonstrating the beneficial effects of exercise in RA, no study to date has investigated the beneficial effects of aerobic exercise on RA patients' cardiovascular risk factors.

With a loss in muscle mass, and subsequent functional limitation and burgeoning disability a characteristic of the disease, RA patients should be encouraged to perform exercises which elicit muscle hypertrophy and strengthening. Several studies have demonstrated the beneficial effects for RA patients of performing muscle strengthening exercises, in particular progressive resistance training (PRT). These improvements include increases in muscle mass, reduction in fat mass, and substantial improvements in physical function (Hakkinen et al., 2005, Lemmey et al., 2009, Marcora et al., 2005). A two-year dynamic strength training programme in early RA patients found significant improvements in muscle strength (19–59%) along with impressive reductions in systemic inflammation, pain, morning stiffness, and disease activity (Häkkinen et al., 2001). These findings suggest that long-term dynamic strength training can significantly improve the physical well-being of RA patients without exacerbating disease activity. Muscle strength gains from PRT programmes can also be maintained over several years of continued training at sufficient intensity (de Jong et al., 2009, Hakkinen, 2004).

It is very clear from the literature detailed above that exercise is beneficial for patients with RA. However, despite this knowledge RA patients remain physically inactive. 68% of RA patients in the UK do not take part in any regular physical activity (Sokka and Hakkinen, 2008). It was also reported that only 13.8% of all RA patients studied reported exercising

three or more times per week, which is the amount of exercise shown to provide health benefits in this population (Andersen et al., 2000, Gregg et al., 2003).

Considering cardiovascular co-morbidity and mortality are increased in patients with RA (Pincus et al., 1984) and the very low levels of cardio-respiratory fitness and physical activity in this population; it is conceivable that poor fitness and physical inactivity may contribute to the cardiovascular morbidity and mortality observed in this population. The existing evidence does not allow an estimate of the relative impact of poor fitness and physical inactivity on CVD in these patients (This is discussed in greater detail in Chapter 6). With a clear gap in the literature the need for research investigating CVD risk factors, cardio-respiratory fitness and the effect of exercise training on CVD health in RA patients is paramount.

1.8 Aims and Objectives

1.8.1 Broad Aim

The broad aim of this thesis is to investigate the association between cardio-respiratory fitness and traditional cardiovascular disease (CVD) risk factors in patients with rheumatoid arthritis (RA).

1.8.2 Specific Objectives

1. To assess the validity and reliability of the Siconolfi step test for estimating cardio-respiratory fitness in patients with RA. In order to investigate the association between cardio-respiratory fitness and traditional CVD risk factors, a valid test to measure cardio-respiratory fitness in RA patients is firstly required (Chapter 3).

2. To determine the association between cardio-respiratory fitness (step test) and traditional cardiovascular disease risk factors in rheumatoid arthritis patients attending a routine rheumatology clinic appointment (Chapter 4).

3. Like poor cardio-respiratory fitness, obesity is also an independent risk for CVD and is often under investigated in RA. The aim of this study was to determine the impact of obesity on RA disease, CVD risk factors and fitness and function (Chapter 5).

4. To investigate whether a short term supervised exercise intervention can improve RA patients overall cardiovascular health and general wellbeing. It is the first study of its kind to assess the effects of exercise on CVD risk factors in a sample of RA patients (Chapter 6).

2 Chapter 2: Methodology

2.1 Participants

A total of 135 RA patients were recruited as participants for the studies presented in this thesis. In the first study 30 RA patients took part in the validation study and acted as their own controls to determine the reliability of the step test. In the second study, data was collected from 100 RA patients who attended a routine rheumatology clinic appointment. Ten RA patients (5 of which also took part in the second study) were recruited and took part in an 8 week supervised exercise programme that formed the basis of study three. All patients had a diagnosis of RA according to the American College of Rheumatology 1987 Criteria for the Classification of Rheumatoid Arthritis (Arnett et al., 1988). All studies included in this PhD thesis received ethical approval by the local research ethics committee. Participants were given verbal and written information about each project and were given a minimum of 48 hours to decide whether or not they wished to take part. Patients who were interested in taking part signed an informed consent on the first day of their assessment according to the declaration of Helsinki (WMA, 2000). Due to the varying nature of each individual study, further details regarding participants are given in the methods section of each respective study.

2.2 Assessments

Full descriptions of assessments common to all studies are given in this section. Where necessary they are presented again to allow the reader to understand the methodology for each independent study. Assessments are categorised into relevant sub headings which include Aspects of Rheumatoid Arthritis, Cardiovascular Risk Factors, Body Composition and Fitness and Function.

2.2.1 Measuring Aspects of Rheumatoid Arthritis

2.2.1.1 Erythrocyte Sedimentation Rate (ESR) & C - reactive protein (CRP)

ESR and CRP are levels used to monitor disease activity and to monitor how well a patient is responding to treatment. ESR is one of the most common laboratory assessments performed on persons with rheumatic diseases. ESR is determined by the rate at which the red blood cells fall in one hour and is reported in $mm \cdot hr^{-1}$. The principle of measurement is the study of the aggregation capacity of red blood cells by telemetry using the TEST1 method (Alifax, Padova, Italy). CRP is an acute phase protein produced by the liver and is elevated when inflammation is present in the body. Like ESR, it is a non-specific test and so does not indicate where in the body inflammation exists. CRP is expressed in $mg \cdot l^{-1}$ and CRP levels > 3 $mg \cdot l^{-1}$ are associated with an increased cardiac risk (Ridker et al., 2002). CRP was measured using an OLYMPUS AU2700 analyzer (Beckman Coulter, Nyon, Switzerland). The test principle is based on the CRP reaction with anti-human CRP antibodies to yield insoluble aggregates. The absorbance of these aggregates is proportional to the CRP concentration in the sample. All blood samples were collected by qualified phlebotomists and analysed by the staff in the clinical biochemistry laboratory at Ysbyty Gwynedd. At this laboratory CRP levels below 5 $mg \cdot l^{-1}$ are expressed as CRP < 5, CRP values above 5 $mg \cdot l^{-1}$ are given a specific number.

2.2.1.2 Disease Activity Score 28 (DAS 28)

The DAS 28 is a measure of disease activity in RA. It includes the joints of the hand, wrist, elbow, shoulder and knee whereby the number of tender and swollen joints are reported (Fransen and van Riel, 2005). Using a 10 cm visual analogue scale (VAS) the patient rated their arthritis during the last week from zero (best ever) to 100 (worst ever). This is known as the patients global health score. These results along with either a score for ESR or CRP were included in a mathematical formula to produce the overall disease activity score (Hensor et al., 2010):

DAS 28 ESR = 0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.70*Ln(ESR) + 0.014*GH

DAS 28 CRP = 0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.36*Ln(CRP+1) + 0.014*GH + 0.96

Where:

t = number of tender joints

sw = number of swollen joints

GH = patients global health rated on the 10 cm VAS

A DAS 28 of > 5.1 implies high disease activity; > 3.2 - < 5.1 indicates moderate disease activity; < 3.2 low disease activity, and < 2.6 remission (Fransen and van Riel, 2005). See Appendix 2 for a copy of the DAS 28 used. Assessments of patient's joints were made by the rheumatologist, rheumatology nurse specialist or the PhD student.

2.2.1.3 Rheumatoid Factor (RF) & Anti Cyclic Citrullinated peptide (anti –CCP)

RF: Rheumatoid factors (RF) are antibodies directed against the fragment crystallizable (Fc) portion of immunoglobulin G and are present in 70% to 90% of people with RA (Nell et al., 2005). However, RF can be found in people without RA or with other autoimmune disorders. The RF is not diagnostic for RA but can be predictive of a more aggressive and erosive disease when compared to RF negative patients (Smolen, 1996).

CCP: In recent years a new test for RA has been developed, the anti-CCP (Schellekens et al., 2000). It measures levels of antibodies that bind citrulline modified proteins. This test is more specific for RA when compared to the RF. The presence of anti-CCP antibodies can be used to predict which patients will develop more severe RA (Schellekens et al., 2000, van Gaalen et al., 2005). Information regarding RA patients RF and CCP was obtained from patients' medical notes. The clinical biochemistry laboratory at Ysbyty Gwynedd uses an aagglutination test to measure RF and an Axis-Shield anti-CCP ELISA to determine CCP.

2.2.1.4 Health Assessment Questionnaire (HAQ)

The HAQ is an international, validated, self reported measure of physical function or functional disability (Fries et al., 1980) that is used in patients with a wide variety of rheumatic diseases, including RA, osteoarthritis, SLE, ankylosing spondylitis and psoriatic arthritis (Bruce and Fries, 2003). HAQ scores less than 1 indicate none or mild disability, a score of 1-2 indicates moderate disability and a score of greater than 2 represents severe disability. The short version of the HAQ was used in this thesis. A copy of this questionnaire can be seen in Appendix 3.

2.2.2 Cardiovascular (CVD) Risk Factors and Global CVD Risk

2.2.2.1 Blood Pressure

Blood pressure was measured twice on the brachial artery using the standard auscultatory technique (3M Littmann Select Stethoscope, S.E., USA; Gold series DS66 Sphygmomanometer, Welch Allyn GmbH and Co, Jungingen, Germany) whilst the patient had been resting in a seated position for approximately 10 minutes. The average of the two measurements is reported throughout.

2.2.2.2 Fasting lipids & Glucose

Patients were required to visit their GP surgery or Ysbyty Gwynedd to have a fasting lipid and glucose blood test within 4 weeks of their study date in study 2 and 1 week of their assessment in study 3. Patients were instructed not to eat or drink anything except water for 10-12 hours before their blood test. Dyslipidemia was classed as a total cholesterol > 5.2 $mmol \cdot l^{-1}$, triglycerides > 1.8 $mmol \cdot l^{-1}$, LDL-c > 3.4 $mmol \cdot l^{-1}$ or if a patient was receiving lipid lowering therapy. Guidelines were taken from the Third Report of the National Cholesterol Education Programme (2002). Blood samples were analyzed in the clinical biochemistry laboratory at Ysbyty Gwynedd using an OLYMPUS AU2700 analyzer (Beckman Coulter, Nyon, Switzerland).

2.2.2.3 Framingham Risk Score

The Framingham Risk Score is a risk assessment tool developed by the Framingham Heart Study that predicts an individual's risk of having a heart attack in the next 10 years (Anderson et al., 1991). A calculation is made using the following information: age, gender, total cholesterol, HDL-c, systolic blood pressure, smoking status and presence of diabetes. A Framingham Risk Score of < 10% represents low risk, 10-20% indicates moderate risk and > 20% represents a high CVD risk. The Framingham risk score was obtained by using the following online Framingham calculator: http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp

2.2.2.4 QRISK2

The QRISK2 CVD score is another tool used to estimate CVD risk (Hippisley-Cox et al., 2008). This is a more recent tool than the Framingham and has been specifically developed for use in the United Kingdom. However, to date the number of publications using the QRISK2 is limited and so both tools are used in this thesis. The advantages of using the QRISK2 is that it contains many of the traditional risk factors included in Framingham (such as age, gender, cholesterol/HDL ratio, blood pressure, diabetes and smoking status) as well as important additional risk factors:

- Self assigned ethnicity
- Family History of premature CVD in a first degree relative under the age of 60
- Deprivation (measured using the Townsend deprivation score) (Woodward et al., 2007)
- Blood pressure treatment
- BMI
- Rheumatoid Arthritis
- Chronic Kidney Disease
- Atrial Fibrillation

The QRISK2 score was obtained by using the following online calculator: http://www.qrisk.org/index.php.

2.2.2.5 Metabolic Syndrome

The metabolic syndrome consists of a constellation of risk factors, primarily abdominal obesity, hyperglycemia, low HDL-c, high triglycerides, and hypertension. The Third Report of the NCEP Adult Treatment Panel (ATP III), published in 2001, is the most widely used definition for metabolic syndrome. A diagnosis of 'metabolic syndrome' requires three of the five criteria listed above.

2.2.3 Body Composition

2.2.3.1 Body Mass Index (BMI)

BMI was calculated by dividing a person's weight measurement (in kilograms) by the square of their height (in meters): BMI = weight (kg) ÷ height^2 (m). WHO guidelines categorise individuals based on their BMI. Adults with a BMI of < 18 kg·m^{-2} are considered underweight, a BMI of 18.5 – 24.9 kg·m^{-2} represents normal weight, whilst a BMI of 25 to 29.9 kg·m^{-2} and > 30 kg·m^{-2} represents overweight and obese individuals respectively (WHO, 2000).

2.2.3.2 Body Fat Percent

Body fat percent was assessed by bioelectrical impedance analysis (BIA) using a Tanita TBF – 305 Body Composition Analyzer (Tanita Corporation, Tokyo, Japan). The procedure for measuring body fat percent involved participants being instructed to remove their shoes and socks and to stand on the scales with each foot placed on the metal plate. BIA then calculated body composition by sending a low, safe electrical signal through the body. BIA operates on the principle that fat mass exhibits greater resistance to the flow of electrical current than fat free mass due to differences in water content (Baumgartner et al., 1990) and has been shown to be a valid measure of percent body fat when compared to the gold standard dual x-ray absorptiometry (DEXA) (Goldfield et al., 2006, Hsieh et al., 2011). Hsieh and colleagues reported a correlation of 0.93 between BIA and DEXA. Optimal values for body fat percentage were given in Figure 1.2.

2.2.3.3 Waist and Hip circumference and Waist hip ratio (Waist:Hip)

Waist circumference was measured midway between the uppermost border of the iliac crest and the lower border of the costal margin (rib cage). Hip circumference was measured around the widest portion of the buttocks. Measurements were taken when the tape was snug but did not compress the skin (WHO, 2008). The waist hip ratio was calculated using the following equation:

Waist:Hip = waist circumference (cm) ÷ hip circumference (cm)

2.2.4 Fitness and Physical Activity

2.2.4.1 Step Test

The Siconolfi Step test was originally developed as a valid and reliable measure of fitness in a healthy population aged 19-70 years (Siconolfi et al., 1985). The step test involves stepping up and down a 10 inch step for three minutes per stage for a maximum of three stages. Stepping rate is kept constant using a metronome. The stepping rates for stages 1-3 are 17, 26, and 34 steps per minute, respectively. Heart rate, measured by telemetry (Model RS400, Polar Electro OY, Finland), is recorded at the end of each three minute stage. If heart rate does not equal or exceed 65% of the age predicted maximum heart rate (220 – age), then the participant is instructed to complete another stage. If the target heart rate (65% of maximum heart rate) is met then the participant continues stepping until the end of that stage. Each stage is separated by a one minute seated rest. The heart rate at the end of the final stage is used to estimate cardio-respiratory fitness ($VO_{2\ max}$) using equations developed by Siconolfi et al. (1985). See Appendix 4.

2.2.4.2 Physical Activity – IPAQ

The purpose of the International Physical Activity Questionnaire (IPAQ) is to provide a set of well-developed instruments that can be used internationally to obtain comparable estimates of physical activity (Craig et al., 2003). The IPAQ assesses physical activity undertaken across a comprehensive set of domains including:

1. Leisure time physical activity

2. Domestic and gardening (yard) activities
3. Work-related physical activity
4. Transport-related physical activity

The IPAQ short form asks about three specific types of activity undertaken in the four domains above. The specific types of activity that are assessed are walking, moderate-intensity activities and vigorous-intensity activities (Hagstromer et al., 2006). Data collected from the IPAQ can be reported as a continuous measure in the form of MET minutes per week or categorical in the form of low, moderate and high levels of physical activity. For a copy of the questionnaire used in this thesis see Appendix 5.

2.3 Data Analysis

For all studies data was inserted into The Statistical Package for Social Sciences version 19.0 (SPSS Inc. Chicago, IL, USA). The Kolmogorov-Smirnov test of normality was used to assess the dispersion of variables. Specific information regarding the statistical analysis performed is explained in greater detail in each respective study.

3 Chapter 3:

Validity and reliability of the Siconolfi Step Test for estimating cardio-respiratory fitness in rheumatoid arthritis patients

3.1 Introduction

Despite cardio-respiratory fitness being widely recognised as an important health indicator, the assessment of cardio-respiratory fitness is often overlooked from a clinical perspective compared with other CVD risk factors (Lee et al., 2010). The criterion measure of cardio-respiratory fitness is maximal oxygen uptake ($VO_{2\ max}$) and its accurate measurement usually requires: expensive testing systems; treadmills or cycle ergometers; suitably trained personnel; and maximal effort from the participant (Davis, 1995). It could be argued, therefore, that the requisites for measuring $VO_{2\ max}$ might preclude routine assessment of cardio-respiratory fitness in patients 'at risk' or incapable of maximal exercise. On the other hand, $VO_{2\ max}$ can be estimated relatively easily from a short bout of submaximal exercise lasting approximately 3 to 9 minutes (Noonan and Dean, 2000).

A wide variety of predictive submaximal exercise protocols are available for use; these include treadmill walking (Bruce et al., 1973, Ebbeling et al., 1991) and cycle ergometry (Astrand and Ryhming, 1954) tests. However, motorised treadmills and cycle ergometers are not always available in a clinical setting. In contrast, step tests that require limited equipment (i.e. step, metronome, heart rate monitor and stop watch), represent an attractive modality for assessing cardio-respiratory fitness in a clinical setting. An advantage of the Siconolfi test over the other step tests is that it may be completed at relatively low levels of exercise. This is very important in low active, clinical groups like patients with RA where exercise intolerance is a feature of their disease. Since predictive exercise tests are population specific the aim of this study was to validate the Siconolfi step test as a measure of cardio-respiratory fitness in patients with RA.

3.2 Methods

3.2.1 Participant Recruitment

With ethical approval (REC reference: 08/WNo01/68), a prospective validation study was conducted in adults attending rheumatology out-patient services of the Betsi Cadwaladr University Health Board (West). Exclusion criteria specific to this study were: a current RA flare; joint surgery in the preceding two months; patients taking beta blockers; established cardiovascular disease; recent upper respiratory tract infection; pregnancy and, history of substance abuse. Consequently, 30 RA individuals (24 females) provided written informed consent and entered the study (Figure 3.1).

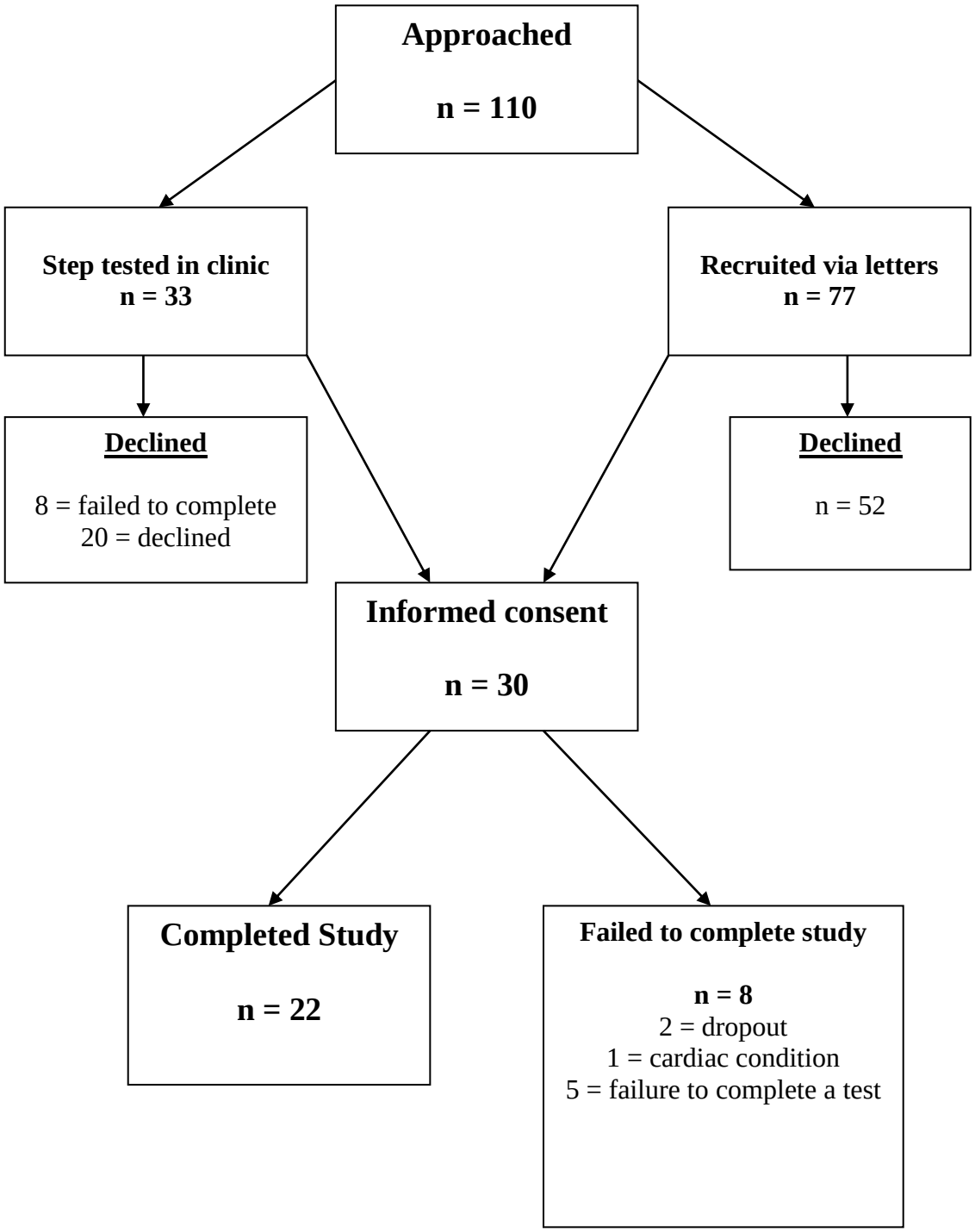

Figure 3.1 Flow chart displaying number of RA patients approached, recruited and completed.

3.2.2 Protocol

Participants were required to attend Llandudno General Hospital on two occasions. The visits were separated by 1 to 3 weeks and scheduled for the same time of day. Participants were instructed to avoid performing strenuous exercise 24 hours prior to testing and not to consume any food, caffeine, alcohol or tobacco in the 3 hours before being assessed.

Visit one: Height and body mass were measured by standard procedures and body mass index (BMI) was calculated ($kg \cdot m^{-2}$). The systolic and diastolic blood pressures were taken by the standard auscultatory technique. Functional status (disability) measures were determined using the Stanford Health Assessment Questionnaire (HAQ) (Fries et al., 1980). Disease activity was assessed using the Disease Activity Score based on 28 joint assessments (DAS 28). Then, each participant undertook the Siconolfi step test which has been described in full detail in chapter 2 (see section 2.2.4.1). Upon completion of the step test, each participant was familiarized with the equipment and procedures for a graded exercise test to volitional exhaustion using a cycle ergometer (Ergomedic 828E, Monark Exercise AB, Sweden); this included familiarization with the Borg categorical scale for rating perceived exertion (RPE) (Borg, 1982). An example of the Borg RPE scale used can be seen in Appendix 6.

Visit two: At the next testing session, each participant repeated the step test. Then, after a 30 minute rest period, a 12 lead ECG was performed at rest. If the ECG trace was normal, participants performed a $VO_{2\ max}$ test. This test is a direct measurement of maximal oxygen uptake (cardio-respiratory fitness). Typically $VO_{2\ max}$ tests can be performed on a treadmill or cycle ergometer. For this project a cycle ergometer was chosen. The test involved pedalling at a constant rate of 50 revolutions per minute (rpm) for two minutes with no resistance added to the flywheel. Thereafter, resistance increased in increments of 25 watts every two minutes, until volitional exhaustion (McArdle et al., 2005). Expired gases and air flow were monitored breath-by-breath using an automated system (800Ergo test, ZAN GmBH, Germany). Heart rate and ratings of perceived exertion (RPE) were measured at the end of every two minute stage (Borg, 1982). It was anticipated that many of these de-conditioned patients would not be able to obtain a true maximal aerobic capacity, defined as a plateau in oxygen consumption during the final stage, maximal heart rate > 85% of age-adjusted predicted maximal heart rate (220–age), respiratory exchange ratio (RER) > 1.10 and ratings of

perceived exertion (RPE) > 17 (Howley et al., 1995, Issekutz and Rodahl, 1961). Therefore, the highest VO_2 recorded during the maximal cycling exercise test was considered to be the $VO_{2\ peak}$ value (Lindstedt et al., 1988).

3.2.3 Data analysis

The primary outcome measure obtained during each of the step tests was estimated $VO_{2\ max}$ (expressed as $ml \cdot kg^{-1} \cdot min^{-1}$), determined using the equations developed by Siconolfi et al. (1985). Outcome measures obtained during the cycling test to volitional exhaustion included; $VO_{2\ peak}$, peak heart rate, RER and ratings of perceived exertion (RPE).

3.2.4 Statistical Analysis

Data was entered into a database and statistical analyses were performed (SPSS, version 19 for Windows, SPSS, Chicago, IL).The mean and standard deviation (SD) were calculated for normally distributed data. The paired t-test was used to establish whether there was a significant systematic bias between test measurements; a two-tailed $p < 0.05$ was considered significant. The concurrent validity of $VO_{2\ max}$ estimated from the Siconolfi step test was assessed using the Bland and Altman technique (Bland and Altman, 1986). The standard error of the estimate (SEE) and the Pearson correlation coefficient (r) was also calculated. The inter-day reproducibility of estimated $VO_{2\ max}$ was assessed using the test-retest within subject coefficient of variation, the Bland and Altman technique, the intraclass correlation coefficient (ICC) and the Pearson correlation coefficient.

3.3 Results

One hundred and ten consecutive patients were contacted over 13 months (July 2009 to August 2010) regarding potential participation in the study. Of these, 80 were unwilling to participate; thus, 30 (24 female) patients were recruited to the study; however 5 recruits (5 female) failed to complete all of the tests and 1 male withdrew due to a previously undiagnosed cardiac complaint (Figure 3.1). The demographic data, disease characteristics and disability scores of the remaining 24 patients are given in Table 3.1.

Table 3.1 Characteristics of 24 patients (19 females and 5 males) with RA participating in the study

	Females	Males	Total Group
Age (years)	54.5 ± 10.5	49.4 ± 9.5	53.4 ± 10.4
Weight (kg)	69.5 ± 15.3	90.0 ± 17.0	73.8 ± 17.5
Height (cm)	164.0 ± 5.6	178.6 ± 6.3	167.1 ± 8.6
BMI ($kg \cdot m^{-2}$)	25.8 ± 5.1	28.3 ± 5.1	26.3 ± 5.1
Resting SBP (mmHg)	125.0 ± 2.0	139.0 ± 7.0	128.0 ± 11.0
Resting DBP (mmHg)	79.0 ± 1.0	86.0 ± 2.0	81.0 ± 6.0
Disease Duration (years)	13.0 ± 1.9	12.8 ± 1.8	13.0 ± 7.3
DAS 28 ESR	2.9 ± 0.3	2.0 ± 0.3	2.7 ± 1.1
HAQ (0-3)	0.6 (range 0 to 1.6)	0.2 (range 0 to 0.4)	0.5 (range 0 to 1.6)

Values are mean ± SD or range. BMI; body mass index; SBP; systolic blood pressure; DBP; diastolic blood pressure; DAS; disease activity score; ESR; erythrocyte sedimentation rate, HAQ; health assessment questionnaire.

The step test was well tolerated, with no adverse events. All of the 24 patients completed both step tests in a single stage. Data for submaximal tests are summarized in Table 3.2. The mean value for $VO_{2\ max}$ estimated at Visit 1 (22.5 ± 4.7 $ml \cdot kg^{-1} \cdot min^{-1}$) was marginally, albeit significantly higher than that at Visit 2 (22.0 ± 4.5 $ml \cdot kg^{-1} \cdot min^{-1}$, $p = 0.049$). The within-subject coefficient of variation for estimated $VO_{2\ max}$ was 5.4%. The Bland-Altman plot (Figure 3.2) of the within subject change for estimated $VO_{2\ max}$ versus the mean for both step tests (i.e. Visit 1 and Visit 2) indicate a small systematic bias (- 0.5 $ml \cdot kg^{-1} \cdot min^{-1}$) between the first and second tests. The 95% limits of agreement (LoA) was ± 2.2 $ml \cdot kg^{-1} \cdot min^{-1}$. The intraclass correlation coefficient (ICC) was 0.97 (95% CI of 0.94 to 0.99) and the Pearson correlation coefficient (r) was 0.97 (95% CI 0.93 to 0.99).

Table 3.2 Heart rate (bpm & % age predicted maximum) and corresponding estimated $VO_{2\ max}$ for 24 patients (19 females and 5 males) that performed the Siconolfi step test.

	Visit 1			Visit 2		
	HR_{Peak}	% Age predicted Max	Estimated $VO_{2\ max}$	HR_{Peak}	% Age predicted Max	Estimated $VO_{2\ max}$
Females	122 ± 12	74 ± 9	21.2 ± 0.9	125 ± 14	75 ± 9	20.8 ± 0.9
Males	120 ± 10	70 ± 4	27.6 ± 1.9	127 ± 14	74 ± 6	26.7 ± 1.8
Total Group	122 ± 11	73 ± 8	22.5 ± 4.7	125 ± 14	75 ± 8	22.0 ± 4.5

Values are mean ± SD. VO_2; oxygen consumption; HR; heart rate, BPM; beats per minute.

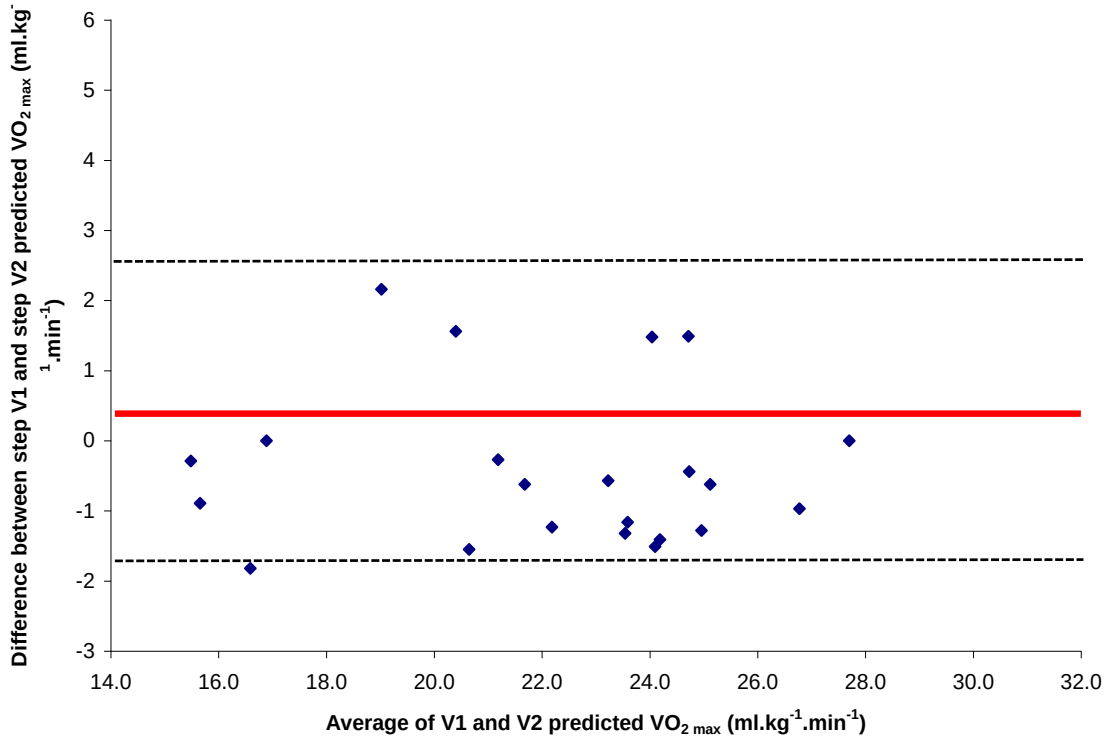

Figure 3.2 Bland-Altman plot of $VO_{2\ max}$ predicted by the Siconolfi step test on visit 1 and visit 2. The mean bias is represented by the solid line and the 95% limits of agreement are represented by the dashed lines.

Two female patients did not complete the graded exercise test for the determination of $VO_{2\ peak}$. Mean peak values for HR, VO_2, RER and RPE of the remaining 22 patients are presented in Table 3.3.

Table 3.3 Physiological variables from the maximal cycling ergometry test in 22 patients (17 females and 2 males).

	Females	Males	Total Group
HR peak	158 ± 13	159 ± 22	158 ± 15
Age predicted max (%)	95 ± 6	93 ± 8	95 ± 7
$VO_{2\ peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	19.2 ± 4.1	22.3 ± 4.0	19.9 ± 4.2
RER_{peak} (VO_2/VCO_2)	1.18 ± 0.12	1.14 ± 0.04	1.18 ± 0.11
RPE (15 point scale)	19 ± 2	18 ± 2	19 ± 2

Values are mean ± SD. RER; respiratory exchange ratio; RPE; ratings of perceived exertion; VO_2; oxygen consumption; VCO_2; carbon dioxide production.

The mean values for $VO_{2\ max}$ estimated from the second step test (Visit 2) and directly measured $VO_{2\ peak}$ were (22.0 ± 4.5) and (19.9 ± 4.2) $ml \cdot kg^{-1} \cdot min^{-1}$, respectively ($p = 0.003$). The Bland-Altman plot of within-subject differences between estimated $VO_{2\ max}$ and directly measured $VO_{2\ peak}$ versus the mean of the two tests is presented in Figure 3.3. The systematic bias between estimated $VO_{2\ max}$ and directly measured $VO_{2\ peak}$ was 2.1 $ml \cdot kg^{-1} \cdot min^{-1}$, the 95% limits of agreement (LoA) was ± 5.7 $ml \cdot kg^{-1} \cdot min^{-1}$, and the SEE was 2.6 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI 2.0 to 3.8 $ml \cdot kg^{-1} \cdot min^{-1}$). The Pearson correlation coefficient (r) was 0.79 (95% CI 0.55 to 0.91). When $VO_{2\ max}$ estimated from the first step test (Visit 1) was used for the same analyses, the findings were found to be very similar (r = 0.77; 95% CI 0.52 to 0.90).

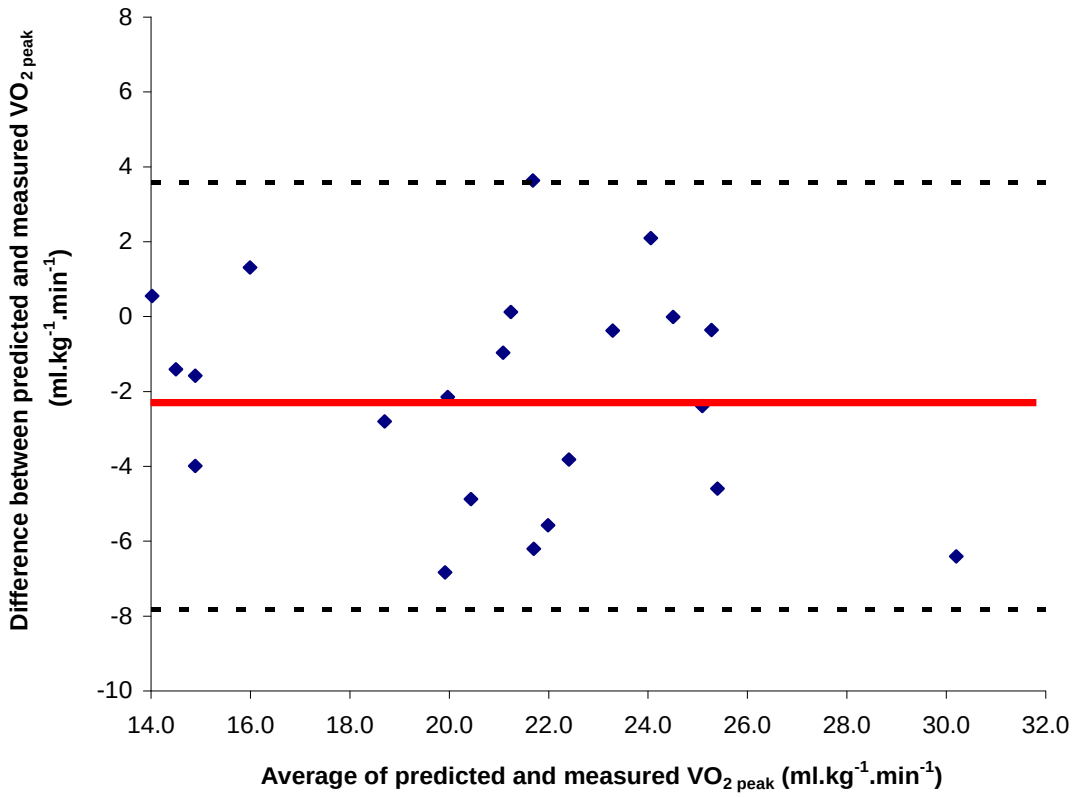

Figure 3.3 Bland-Altman plot of $VO_{2\ peak}$ measured during the cycle test and $VO_{2\ max}$ predicted by the Siconolfi step test (visit 2). The mean bias is represented by the solid line and the 95% limits of agreement are represented by the dashed lines.

3.4 Discussion

The findings presented here demonstrate that administration of the Siconolfi step test provides a valid and reproducible estimation of cardio-respiratory fitness ($VO_{2\ max}$) in routine clinical practice. These findings are important; $VO_{2\ max}$, the measure of an individual's cardio-respiratory fitness, is a strong independent predictor of mortality in asymptomatic individuals as well as in clinical patients. Low cardio-respiratory fitness carries the same or higher strength of association or risk for mortality as routinely measured clinical risk factors such as hypertension, dyslipidemia, diabetes, family history of CVD and smoking (Lee et al., 2010). Furthermore, meta-analysis indicates that a cardio-respiratory fitness below ~ 28 $ml \cdot kg^{-1} \cdot min^{-1}$ results in substantially higher rates of all-cause mortality and CHD/CVD events in healthy persons (Kodama et al., 2009). This is alarming considering the average cardio-respiratory fitness level of the RA patients in this investigation was 19.9 ± 4.2 $ml \cdot kg^{-1} \cdot min^{-1}$. Despite all the evidence to support the use of cardio-respiratory fitness as an additional clinical measure for identifying CVD risk, the assessment of $VO_{2\ max}$ is usually not performed in most, if not all, clinical practices.

Direct measurement of $VO_{2\ max}$ may place certain patient groups like RA patients at risk and is not always practical in many healthcare settings. In contrast, estimation of $VO_{2\ max}$ from submaximal testing appears to have greater applicability, particularly for assessment of cardio-respiratory fitness in a clinical setting. Submaximal predictive tests like the Siconolfi step test provide a simple, safe and valid estimate of $VO_{2\ max}$. Originally developed to estimate $VO_{2\ max}$ in apparently healthy individuals (Siconolfi et al., 1985), the purpose of the present study was to determine if administration of the Siconolfi step test provided a valid and reliable estimate of $VO_{2\ max}$ in patients with RA, a population with increased CVD risk and low exercise tolerance.

The findings presented in this chapter indicate that $VO_{2\ max}$ estimation from the Siconolfi step test was in reasonable agreement with the criterion measure, i.e. directly measured $VO_{2\ peak}$. However, there was a small significant positive bias in the estimated versus the actual $VO_{2\ max}$. The bias ± 95% LoA indicated that the Siconolfi step test could potentially overestimate $VO_{2\ max}$ by 3.6 $ml \cdot kg^{-1} \cdot min^{-1}$ in RA patients. Furthermore, the overall standard error of estimate of ± 2.6 $ml \cdot kg^{-1} \cdot min^{-1}$ means that the accuracy of the $VO_{2\ max}$ estimation in RA

patients with an actual $VO_{2\ max}$ ranging from 12.9 to 27.0 $ml \cdot kg^{-1} \cdot min^{-1}$ was approximately 10 to 20%.

An estimated value for $VO_{2\ max}$ that is higher than the directly measured $VO_{2\ peak}$ may reflect differences between stepping and cycling exercise. It is possible that local muscle fatigue experienced by those unaccustomed to cycling exercise may have resulted in some of the maximal exercise tests being terminated before attainment of 'true' $VO_{2\ max}$ (Midgley et al., 2009). However, other indicators of maximal effort concomitant with $VO_{2\ max}$ (Howley et al., 1995), such as attaining a heart rate within 15 bpm of the age-predicted maximal value, a respiratory exchange ratio of greater than 1.10, and RPE greater than 17, were achieved in RA patients. This suggests that the current patients did exercise at or close to their maximal effort (Poole et al., 2008). Another possible explanation for overestimation of cardio-respiratory fitness by the step test may be related to the timing of tests performed on visit 2. However, the short duration of the step test (i.e. 3 minutes) and the longer rest period (i.e. 30 minutes minimum) between tests argue against this.

The test-retest repeatability of the estimated $VO_{2\ max}$ via the step test in the current study was excellent. The Pearson correlation coefficient and ICC indicated a very high correlation between the two step tests. However, there was a small but significant inter-trial bias (- 0.5 $ml \cdot kg^{-1} \cdot min^{-1}$). The 95% LoA (± 2.2 $ml \cdot kg^{-1} \cdot min^{-1}$) is considered acceptable. Thus, an increase in estimated $VO_{2\ max}$ of approximately 2.5 $ml \cdot kg^{-1} \cdot min^{-1}$ or above following an exercise training intervention could be considered a change that is due to factors other than chance. In RA patients, this would equate to an increase in cardio-respiratory fitness of around 20% for the individual with the lowest $VO_{2\ max}$ whereas the person with the highest $VO_{2\ max}$ would experience a 10% increase.

We know of only one other study that has investigated the validity and test-retest reproducibility of the Siconolfi step test in a patient group. Marcora and colleagues (Marcora et al., 2007) found that the Siconolfi step test was reasonably valid and highly reliable in patients with well controlled systemic lupus erythematosus (SLE). Compared to the patients in the present study, the SLE patients in that study were younger, weighed slightly less, had similar BMI, and had a higher directly measured $VO_{2\ max}$ relative to body mass. The validity and reliability analyses for our study compare well to those of Marcora et al. (2007).

The most concerning, but unsurprising finding, of the present study was the very low value for the directly measured $VO_{2\ max}$ in the RA patients. Previous reports indicated that $VO_{2\ max}$ may be 20 to 30% lower in RA patients compared with age matched healthy controls (Chang et al., 2009, Ekdahl and Broman, 1992, Harkcom et al., 1985, Minor et al., 1989). A major determinant of $VO_{2\ max}$ is the degree of physical activity over recent weeks and months. Evidence suggests that approximately 68% of RA patients in the UK are physically inactive (Sokka and Hakkinen, 2008); therefore, compromised cardio-respiratory fitness in patients with RA is hardly surprising. Despite knowing that increased incidence of CVD-related morbidity and mortality is a common feature of RA (Avina-Zubieta et al., 2008, Pincus et al., 2001), the relative contributions of physical inactivity, traditional risk factors, and high grade systemic inflammation to the exacerbated CVD risk in this population remains unclear (Metsios et al., 2009, Sattar et al., 2003, Solomon et al., 2010, Stevens et al., 2005). However, exercise is recognized as useful adjunct treatment for RA (Cooney et al., 2011), although the relationships between cardio-respiratory fitness, exercise training and CVD risk factors in RA patients requires more research (Metsios et al., 2009).

The strengths and weaknesses of this study warrant comment. The Siconolfi step test is easy to administer, requires minimal equipment, and is relatively quick since it can be completed at low levels of exercise. Thus, there is considerable potential for its use as a clinical tool for routine assessment of cardio-respiratory fitness in patients with RA and other clinical populations who are at risk of developing CVD. All of the patients studied here completed the test after the first stage. Although fatigue, pain, limited joint mobility and impaired muscle strength are all common features of RA (Arnett et al., 1988, Ekdahl and Broman, 1992) the step test was reasonably well tolerated by patients in this study. Potential sources of error in the current study included: prediction of maximum heart rate from the 220-age formula; assumption of a linear relationship between heart rate and VO_2; and, the individual's ability to maintain the correct stepping tempo; all of which are common to submaximal exercise testing (Howley et al., 1995). Potential fatigue resulting from the $VO_{2\ max}$ test taking place after the step test was minimised by ensuring that at least 30 minutes rest was provided and that resting ECG was normal after the 3 minutes of the step test exercise. Due to RA being primarily a joint disease we specifically chose to compare the step test to a cycling-based $VO_{2\ max}$ test. Even though cycling is not a weight-bearing activity, it may put the knee joint under a similar strain/range of movement than a walking-based test. A treadmill-based $VO_{2\ max}$ test may have resulted in a higher $VO_{2\ max}$ than what was obtained in this study

(Shephard, 1984). Another limitation is the modest sample size; however, it was sufficient to meet the study objectives, with suitable measures of validity and test-retest reliability being observed.

3.5 Conclusion

The present study is the first to demonstrate that the Siconolfi step test is a reliable method for assessing cardio-respiratory fitness in an RA population. In light of considerable epidemiological evidence that supports the cardio protective effects of regular physical activity and cardio-respiratory fitness; the current findings indicate a role for simple, clinically available physiological estimation of $VO_{2\ max}$. Another important finding is the very low cardio-respiratory fitness in patients with RA. It is well known that this group is twice as likely to die from a CVD related event when compared to the general population (Avina-Zubieta et al., 2008). Therefore, following on from the current study it is believed that patients with RA and other chronic diseases with increased risk of CVD should have their cardio-respiratory fitness measured as part of their cardiovascular screening and advised to maximise as part of any long term management plan. This is achievable using the step test in RA.

4 Chapter 4:

Association between cardio-respiratory fitness (step test) and traditional cardiovascular disease risk factors in rheumatoid arthritis

4.1 Introduction

The measurement of cardio-respiratory fitness as part of routine clinical care is generally nonexistent in rheumatology. One reason for this may be that a simple method to assess fitness in a clinical setting did not exist. Now that the step test was shown to be a very simple tool to assess cardio-respiratory fitness in this population, this next chapter aims to highlight the potential importance of such a measure in routine clinical practice.

Rheumatoid arthritis (RA) is a chronic systemic immune and inflammatory disease that is associated with a 50-60% increased risk of mortality from CVD compared to the general population (Avina-Zubieta et al., 2008). It is believed that both traditional CVD risk factors and novel risk factors such as inflammation contribute to the increased risk of atherosclerotic CVD in patients with RA. Furthermore, other precipitating factors, such as persistent low levels of physical activity (Lee et al., 2000, Metsios et al., 2009, Warren et al., 2010) and poor cardio-respiratory fitness (Blair et al., 1989, Myers et al., 2002) likely contribute.

Studies involving RA patients have revealed significantly reduced cardio-respiratory fitness levels with reductions of 20-30% being reported in research by Stenstrom and Minor (2003). Average $VO_{2\ max}$ values obtained from a group of female RA patients equalled 22 $ml \cdot kg^{-1} \cdot min^{-1}$ (Minor and Hewett, 1995). The same poor level of cardio-respiratory fitness was also observed in our cohort in the previous chapter. Comparing these poor values to healthy adults of similar age confirms that RA patients have a significantly reduced cardio-respiratory fitness level (Stenstrom and Minor, 2003, Mitros et al., 2011, McKenzie et al., 2011, Schulman et al., 1996).

To our knowledge only one study exists that has examined the associations between physical activity and traditional CVD risk factors in patients with RA (Metsios et al., 2009). Reduced physical activity was associated with increased systolic blood pressure, total cholesterol, and low density lipoprotein. There are no studies that have examined the association between

classical CVD risk factors such as hypertension and dyslipidemia and cardio-respiratory fitness. Therefore, the aim of the present study was to determine whether poor cardio-respiratory fitness is in fact associated with a worse CVD risk factor profile and whether this also associates with worse RA disease in a typical RA population.

4.2 Methods

4.2.1 Participant Recruitment

With ethical approval (REC reference: 10/WNo01/11) 100 consecutive adults attending rheumatology out-patient services of the Betsi Cadwaladr University Health Board (West) were recruited. Patients diagnosed with RA and who attended the rheumatology clinic, were considered as potential participants for this study. Exclusion criteria were: patients pregnant or breastfeeding, taking a beta blocker, suffering from dementia, neurological impairment, cancer, or if they had a musculoskeletal impairment that prevented them from being able to do the step test. Patients with unstable chronic and terminal illness were also excluded.

4.2.2 Protocol

Patients attending their routine rheumatology appointment were invited to take part in this testing session. Interested patients were assessed in parallel to their rheumatology medical or nurse practitioner clinic appointment. On the day of this appointment the following measures were assessed in this approximate order:

1. *RA Related Factors*

Patients were required to have a recent blood test (< 4 weeks) for the assessment of inflammation (ESR and CRP). Functional status (disability) was determined using the Stanford Health Assessment Questionnaire (HAQ). Disease activity was assessed using the Disease Activity Score 28 (DAS 28) and patients rated their arthritis over the last week (global health) and their current level of pain using a 10 cm visual analogue scale.

2. *CVD risk Factors*

Whilst patients were rested systolic and diastolic blood pressures were taken by the standard auscultatory technique. Patients were required to give a fasting blood sample within four weeks of the testing session to assess fasting lipids and fasting glucose. Detailed information regarding patients smoking status, family history of heart disease and current medication was obtained using a cardiovascular questionnaire.

3. *Body Composition*

Height and body mass were measured by standard procedures and body mass index (BMI) was calculated ($kg \cdot m^{-2}$). Bioelectrical impedance analysis was used to assess body fat

percentage (Tanita corp., Tokyo, Japan) and waist and hip circumference was also measured to determine waist hip ratio (Waist:Hip).

4. Fitness and physical activity

Patients completed the International Physical Activity Questionnaire (IPAQ) – short form to assess their level of physical activity in the last 7 days. Once completed, each participant undertook the Siconolfi step test, which has been described in length in chapter 2 (see section 2.2.4.1). Each individual's $VO_{2\ max}$ was estimated from the exercise heart rate at the end of the test according to established equations (see Appendix 4).

4.2.3 Statistical Analysis

All data analysis was performed using the Statistical Package for Social Sciences version 19.0 (SPSS Inc. Chicago, Illinois, USA). The Kolmogorov – Smirnov test of normality was used to assess the distribution of the variables. Non parametric tests were performed on data that was not normally distributed (CRP, HAQ, glucose).

Pearson's correlation coefficient (parametric), Spearman's correlation coefficient (non parametric), logistic regression analysis and ANCOVA were performed to assess the association between fitness and RA disease related factors, body composition, CVD risk factors and global CVD risk scores. Hierarchical multiple regression was performed to determine what factors best predict fitness.

Participants were categorised according to their performance on the step test (able to do step test **'ABLE'** and unable to do the step test **'UNABLE'**). MANOVA was used to assess the differences between the step ability groups for RA disease, body composition and CVD risk factors. If MANOVA revealed a significant difference, the dependent variables were considered separately using a Boneferroni adjusted alpha level (0.05/number of dependent variables). Binary logistic regression analysis was used to determine the impact of certain factors on step ability. Chi squared analysis was used to assess the association between step ability groups and all other categorical variables – RA disease, body composition, CVD risk and physical activity. Discriminant function analysis was performed to determine the best predictor of step ability. Statistical significance was set at $p < 0.05$ for all analyses unless stated otherwise.

4.3 Results

100 RA patients (69% female) were included in this investigation (mean ± SD; age 59.6 ± 10.2 years; disease duration 10.4 ± 9.1 years). RA patients had well controlled disease with low levels of inflammation (ESR = 16.1 $mm \cdot hr^{-1}$; CRP = 12.7 $mg \cdot l^{-1}$), disease activity (DAS 28 ESR = 2.7) and disability (HAQ = 0.87). Detailed information regarding RA patients' disease related factors is given in Table 4.1.

Table 4.1 Description of RA patient's disease related factors.

Patient Characteristic	Mean or %	SD
Age (years)	59.6	10.2
Female (%)	69	
RA variables		
RA duration (years)	10.4	9.1
RA ≤ 2 yrs (%)	15	
RA 2-5 yrs (%)	18	
RA 5-10 yrs (%)	31	
RA >10 yrs (%)	36	
ESR ($mm \cdot hr^{-1}$)	16.1	12.7
CRP ($mg \cdot l^{-1}$)	12.7^{+}	17.5
CRP < 5 $mg \cdot l^{-1}$ (%)	49	
CRP > 5 ($mg \cdot l^{-1}$)	21.2*	21.5
Rheumatoid factor positive (%)	72	
CCP positive (%)	79	
DAS 28 ESR	2.7	1.4
DAS 28 CRP	2.8	1.1
VAS arthritis (0-100)	31.9	23.8
Pain (0-100)	22.9	27.6
HAQ (0-3)	0.87	0.76

Values are mean ± SD or percentage of patients (%), N = 100. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, CCP; cyclic citrullinated peptide, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire. *mean CRP of patients with a CRP > 5 $mg \cdot l^{-1}$, $^{+}$CRP = 4 was used for CRP values < 5.

The majority of patients were being treated with DMARDs such as Methotrexate (66%), Leflunomide (16%), Sulphasalazine (13%) and Hydroxychloroquine (7%) with only 19% of patients receiving biologic therapy. 60% of patients were receiving monotherapy and 32% of patients were receiving combination therapy (28% of patients receiving a combination of two, 4% of patients receiving a combination of three). Eight percent of patients were not being treated with DMARDs. In terms of steroid exposure, 43% had never taken any steroids,

44% had taken steroids in the past and 13% of patients were currently taking steroids. The average (range) current steroid daily dose was 7.9 (2.5 – 20) mg. Of the steroid users 63%, 15% and 23% were taking average daily doses of ≤ 7.5 mg, 10 mg and ≥ 15 mg, respectively.

Based on their mean BMI, both females and males were categorised as overweight (BMI > 25), with a full breakdown of body composition of the RA patients shown in Table 4.2. In fact, 68% of the RA patients were over fat or obese according to their body fat percent and the prevalence of being overweight or obese was much higher in female RA patients (75%) than in males (52%).

Table 4.2 Body composition of RA patients.

Patient characteristic	Total (n = 100)	Females (n = 69)	Males (n = 31)
Weight (kg)	74.5 ± 15.9	71.50 ± 15.0	79.8 ± 15.8
BMI ($kg \cdot m^{-2}$)	27.9 ± 5.7	28.2 ± 6.0	27.1 ± 5.1
BMI < 25 (%)	39	39	39
BMI 25-< 30 (%)	34	30.5	42
BMI > 30 (%)	27	30.5	19
Body Fat (%)	37.5 ± 14.5	43.6 ± 12.9	24.2 ± 7.2
Body fat normal (%)	32	25	48
Body fat overfat (%)	22	17	32
Body fat obese (%)	46	58	20
Waist (cm)	91.2 ± 13.2	87.5 ± 11.8	97.6 ± 11.6
Hip (cm)	100.7 ± 11.3	100.9 ± 12.4	100.1 ± 8.6
Waist:Hip	.90 ± .07	.87 ± .05	.97 ± .05

Values are mean ± SD or percentage of patients (%), N = 100. BMI; body mass index.

Overall the traditional cardiovascular risk factors and associated physiological variables were found to be within normal ranges (described in section 1.2.1.1). However, on the day of the assessment 66% of patients were found to be hypertensive and 69% of patients had dyslipidemia (Table 4.3).

Table 4.3 Cardiovascular risk factors (CVD) of RA patients.

Patient Characteristic	Mean or %	SD
Hypertensive (%)*	**66**	
SBP (mmHg)	139.6	20.8
DBP (mmHg)	80.9	11.6
Anti hypertensive medication (%)	32[†]	
Dyslipidemia (%)*	**69**	
TC ($mmol \cdot l^{-1}$)	5.2	1.1
TG ($mmol \cdot l^{-1}$)	1.5	0.8
LDL-c ($mmol \cdot l^{-1}$)	3.1	1.0
HDL-c ($mmol \cdot l^{-1}$)	1.5	0.5
TC/HDL ratio	3.8	1.8
Anti hyperlipidemia medication (%)	28[#]	
Diabetics (%)	**8**	
Glucose ($mmol \cdot l^{-1}$)	5.2	1.0
Smoking status		
Current smoker (%)	23	
Ex Smoker (%)	46	
Family history CVD (%)	**27**	

Values are mean ± SD or percentage of patients (%), N = 100. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein, MetS; metabolic syndrome.*Hypertensive; SBP > 140 mmHg, DBP > 90 mmHg or on medication, Dyslipidemia; High TC > 5.2, LDL-c > 3.4, TG > 1.8 or on medication. [†] Central alpha agonist (n=1), Diuretic (n=5), Calcium antagonist (n=8), Ace inhibitor (n=18). [#]Statin (n=27), Fibrate (n=1).

Using some of the above physiological measures (e.g. blood pressure, TC, BMI), global CVD risk scores were calculated. The Framingham 10 year CVD risk was moderate for females (> 10%) and high for males (> 20%). The QRISK2 reported an even higher average 10 year CVD risk (19.8%) which was also moderate for females and high for males. Forty-one percent of RA patients were classified as having MetS based on the clustering of risk factors (see section 2.2.2.5). See Table 4.4 for global CVD risk score data.

Table 4.4 Global CVD risk scores in patients with RA.

Patient Characteristic	Mean or %	SD
Framingham 10 year risk (percent)	15.9	10.4
Framingham risk – females (percent)	11.8	7.1
Framingham risk – males (percent)	26.1	10.0
QRISK2 (percent)	19.8	13.5
QRISK2 – females (percent)	14.9	10.2
QRISK2 – males (percent)	30.9	13.7
Metabolic syndrome (NCEP) (%)	41	

Values are mean ± SD, N = 100. NCEP; national cholesterol education programme.

4.3.1 Fitness

Of the 100 RA patients, 65% were able to complete the step test. Their cardio-respiratory fitness was predicted using age, gender, weight and their exercise heart rate. Further details of the patients unable to complete the step test are provided in section 4.3.2. Total predicted fitness (n=65) was 22.0 ± 5.9 $ml \cdot kg^{-1} \cdot min^{-1}$ and was 20.3 ± 4.8 $ml \cdot kg^{-1} \cdot min^{-1}$ and 26.3 ± 6.2 $ml \cdot kg^{-1} \cdot min^{-1}$ for females and males, respectively (Figure 4.1). Results from the International Physical Activity Questionnaire (IPAQ) showed that 55% of patients were classed as inactive, 35% were moderately active with only 10% of patients self reporting a high level of physical activity.

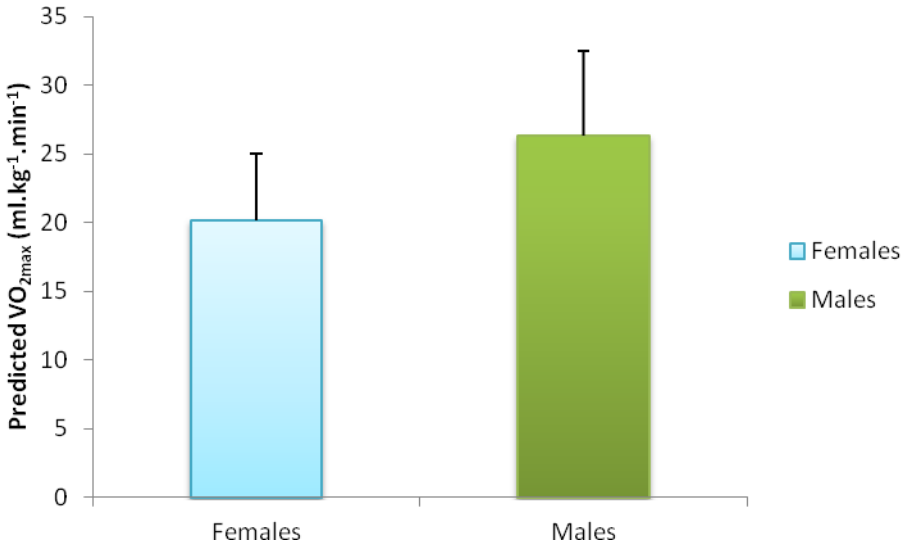

Figure 4.1 Predicted $VO_{2\,max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) for female and male RA patients (N = 65). Values are mean ± SD.

The association between cardio-respiratory fitness and the other variables measured; RA related factors, body composition and CVD risk factors are analysed below (see Tables 4.5-4.7).

4.3.1.1 RA Factors

In relation to the RA disease related factors cardio-respiratory fitness correlated significantly with HAQ scores, with better cardio-respiratory fitness associated with less reported disability. Cardio-respiratory fitness did not correlate with the other RA disease related factors when controlling for age and gender (see Table 4.5).

Table 4.5 Associations between cardio-respiratory fitness and RA disease related factors.

RA Characteristic	Correlation	*P*
Disease Duration (years)	0.027	0.909
ESR ($mm \cdot hr^{-1}$)	-0.039	0.871
CRP ($mg \cdot l^{-1}$)	-0.065	0.609
Tender Joints (n)	0.017	0.892
Swollen Joints (n)	0.091	0.473
DAS 28 ESR	-0.072	0.763
DAS 28 CRP	-0.100	0.674
VAS arthritis (0-100)	0.112	0.640
Pain (0-100)	0.006	0.981
HAQ (0-3)	-0.255	0.040*

Values are Pearson's or Spearman's correlations controlling for age and gender, N = 65.
ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, CCP; cyclic citrullinated peptide, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

4.3.1.2 Body Composition

Cardio-respiratory fitness correlated significantly with all measures of body composition (weight, BMI, body fat percent, waist circumference, hip circumference and waist:hip) when adjusting for age and gender (see Table 4.6). Waist circumference was strongly associated with level of cardio-respiratory fitness, whilst wasit:hip was poorly associated with level of cardio-respiratory fitness.

Table 4.6 Associations between cardio-respiratory fitness and body composition.

Body Composition	Correlation	*P*
Weight (kg)	-0.641	0.000*
BMI ($kg \cdot m^{-2}$)	-0.614	0.000*
Body fat percent (%)	-0.481	0.000*
Waist (cm)	-0.651	0.000*
Hip (cm)	-0.584	0.000*
Waist: Hip	-0.254	0.045*

Values are Pearson's correlations controlling for age and gender, N = 65. BMI; body mass index

Cardio-respiratory fitness was 24% lower in patients who were obese (using percent body fat) compared to patients who were not obese (19.1 ± 4.9 $ml \cdot kg^{-1} \cdot min^{-1}$ versus 23.7 ± 5.8 $ml \cdot kg^{-1} \cdot min^{-1}$, $p = 0.002$). Using ANCOVA, with age, gender and disease duration as covariates, obesity remained a significant and independent predictor of cardio-respiratory fitness ($F_{1, 60} = 8.3$; $p < 0.01$).

4.3.1.3 CVD Risk Factors

Cardio-respiratory fitness correlated significantly with diastolic blood pressure and triglycerides but did not correlate with the other CVD risk factors or Global CVD risk scores (see Table 4.7).

Table 4.7 Associations between cardio-respiratory fitness and CVD risk factors.

CVD Risk Factors	Correlation	*P*
SBP (mmHg)	-0.054	0.675
DBP (mmHg)	-0.344	0.006*
TC ($mmol \cdot l^{-1}$)	-0.163	0.285
TG ($mmol \cdot l^{-1}$)	-0.270	0.043*
LDL-c ($mmol \cdot l^{-1}$)	-0.045	0.747
HDL-c ($mmol \cdot l^{-1}$)	0.024	0.874
Glucose ($mmol \cdot l^{-1}$)	-0.228	0.115
Global CVD Risk Score		
Framingham risk (%)	-0.067	0.662
QRISK2 (%)	-0.165	0.278

Values are Pearson's or Spearman's correlations controlling for age and gender, N = 65. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

There was also no significant association between cardio-respiratory fitness and family history of heart disease (OR = 1.06, 95% CI = 0.96-1.17; p = 0.275), diabetes (OR = 1.07, 95% CI = 0.93-1.24; p = 0.321), hypertension (medication or high blood pressure) (OR = 1.08, 95% CI = 0.98-1.18; p = 0.112), dyslipidemia (medication or high cholesterol) (OR = 1.08, 95% CI = 0.98-1.19; p = 0.105), smoking status (OR = 0.94, 95% CI = 0.86-1.04; p = 0.212), metabolic syndrome (OR = 1.07, 95% CI = 0.97-1.18; p = 0.172) or number of CVD risk factors (OR = 0.96, 95% CI = 0.87-1.07; p = 0.479).

Based on the above associations hierarchical multiple regression was used to assess the ability of two measures (body fat percent, HAQ) to predict level of cardio-respiratory fitness. HAQ was entered at step 1, explaining 3.7% of the variance in fitness levels (R square change 0.037). After entry of body fat percent at step 2 the total variance explained by the model as a whole was 30.2% (F (2,62) = 13.43, p < 0.001). Body fat percent explained an additional 26.6% of the variance in fitness, after controlling for HAQ, R square change 0.266, (F (1,62) = 23.59, p < 0.001). In the final model, only body fat percent was a significant predictor of cardio-respiratory fitness (beta -0.53, p < 0.001).

4.3.2 "Step Ability"

Of the 35 RA patients that were unable to complete the step test, 66% were female and 34% were male. The reasons given by the participants that were unable to complete the step test were 88% pain (in the hip, knee, ankle/foot), 31% unbalanced/weakness and 23% breathlessness. In order to analyse this population in more detail a comparison of the **'Unable group'** was made with those patients who were **'able'** to complete the step test. Differences between females and males were also analysed (full description of gender specific results are detailed in Appendix 7). The pertinent findings are outlined below.

4.3.2.1 RA factors

Differences in RA disease variables between the two step ability groups were analysed. Patients unable to complete the step test rated their arthritis as worse, more painful and disabling than those that were able to complete the step test. **VAS arthritis** (F (1, 96) = 23.4, p = 0.000, partial eta squared = 0.19), **pain** (F (1, 96) = 10.4, p = 0.002, partial eta squared = 0.10) and **HAQ** (F (1, 96) = 36.4, p = 0.000, partial eta squared = 0.28) were the only

variables to reach significance, using a Bonferroni adjusted alpha level of 0.005 between the two groups (see Table 4.8). Similar results were observed for the female RA patients. However, no differences in RA disease related factors were observed between males who were able or unable to complete the step test (see Appendix 7).

Table 4.8 RA characteristics of unable and able patients.

RA Characteristic	Unable (n = 35)	Able (n = 65)	*P*
Age (years)	62.2 ± 8.4	58.2 ± 10.9	0.062
Disease duration (years)	11.0 ± 10.5	10.1 ± 8.4	0.665
ESR ($mm \cdot hr^{-1}$)	19.9 ± 13.4	14.1 ± 11.9	0.017
CRP ($mg \cdot l^{-1}$)	17.9 ± 21.6	8.8 ± 14.8	0.010
Tender joints (n)	1.8 ± 3.1	2.1 ± 4.5	0.823
Swollen joints (n)	0.6 ± 1.6	0.8 ± 2.3	0.792
VAS arthritis (0-100)	46.4 ± 24.1	24.3 ± 19.9	0.000*
Pain (0-100)	34.9 ± 31.5	16.8 ± 23.4	0.002*
DAS 28 ESR	3.1 ± 1.2	2.5 ± 1.5	0.022
DAS 28 CRP	3.0 ± 1.1	2.6 ± 1.2	0.041
HAQ (0-3)	1.5 ± 0.7	0.6 ± 0.6	0.000*

*Significant at Bonferroni adjusted alpha level of $P < 0.005$, Values are mean ± SD, N = 100. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, CCP; cyclic citrullinated peptide, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

To determine the impact of RA factors on the likelihood that patients would not complete the step test, binary logistic regression analysis was performed. The model contained 10 independent variables (age, gender, disease duration, ESR, CRP, VAS arthritis, pain, HAQ, tender joints, swollen joints). The model explained between 40.5% and 56.2% of the variance in step ability, and correctly classified 84.7% of cases. Only 3 independent variables made a unique significant contribution to the model. **HAQ** (OR = 5.65, 95% CI = 1.75-18.21; p = 0.004), **VAS arthritis** (OR = 1.04, 95% CI = 1.00-1.08; p = 0.050) and **Tender joints** (OR = 0.79, 95% CI = 0.64-0.98; p = 0.033). The strongest predictor of being able to complete the step test was the **HAQ** score.

Step ability was not associated with DMARD group (methotrexate, other DMARD, biologic) (χ^2 (2, n = 100) = 2.05, p = 0.358, phi = 0.14), CRP group (CRP < 5 or CRP > 5) (χ^2 (1, n = 100) = 3.03, p = 0.082, phi = 0.17), steroid exposure (χ^2 (2, n = 100) = 0.35, p = 0.554, phi = -0.09), presence of rheumatoid factor (χ^2 (4, n = 100) = 4.36, p = 0.113, phi = 2.09) or CCP positivity (χ^2 (4, n = 100) = 5.26, p = 0.072, phi = 0.23).

4.3.2.2 Body Composition

All body composition variables except weight were observed to be different between the two step ability groups when using a Bonferroni adjusted alpha level of 0.008 (adjusting for age and gender); **Weight** (F (1, 95) = 7.0, p = 0.009, partial eta squared = 0.07), **BMI** (F (1, 95) = 15.4, p = 0.000, partial eta squared = 0.14), **body fat percent** (F (1, 95) = 12.0, p = 0.001, partial eta squared = 0.11), **waist circumference** (F (1, 95) = 15.7, p = 0.000, partial eta squared = 0.14), **hip circumference** (F (1, 95) = 8.7, p = 0.004, partial eta squared = 0.08) and **waist:hip** (F (1, 95) = 9.5, p = 0.003, partial eta squared = 0.09). Inspection of the mean scores indicated that patients unable to complete the step test had a less favourable body composition (see Table 4.9 below). When examining the groups according to gender, male RA patients showed no difference in body composition (See Appendix 7).

Table 4.9 Body composition of unable and able patients.

Body Composition	Unable (n = 35)	Able (n = 65)	*P*
Weight (kg)	79.10 ± 18.23	71.50 ± 13.60	0.009
BMI ($kg \cdot m^{-2}$)	30.40 ± 6.60	26.29 ± 4.17	0.000*
Body Fat (%)	41.91 ± 17.60	35.30 ± 12.10	0.001*
Waist (cm)	97.20 ± 13.13	87.44 ± 11.12	0.000*
Hip (cm)	104.52 ± 12.14	98.06 ± 9.05	0.004*
Waist:Hip	0.92 ± 0.07	0.88 ± 0.06	0.003*

*Significant at Bonferroni adjusted alpha level of $P < 0.008$. Values are mean ± SD, N = 100, BMI; body mass index.

To determine the impact of body composition variables on the likelihood that patients would not complete the step test binary logistic regression analysis was performed. The model contained 5 independent variables (weight, BMI, waist, hip and body fat percent). The model explained between 24.6% and 34% of the variance in step ability, and correctly classified 74.7% of cases. Only 3 independent variables made a unique significant contribution to the model, **BMI** (OR = 1.48, 95% CI = 1.05-2.09; p = 0.024), **waist circumference** (OR = 1.45, 95% CI = 1.03-1.27; p = 0.012) and **weight** (OR = 0.86, 95% CI = 0.78-0.95; p = 0.003). The strongest predictor was **BMI**.

Patients unable to complete the step test had a greater prevalence of obesity. Step ability was associated with BMI category (χ^2 (2, n = 100) = 10.69, p = 0.005, phi = 0.33) and body fat percentage category (χ^2 (2, n = 100) = 6.66, p = 0.036, phi = 0.26).

4.3.2.3 CVD Risk Factors

There were no significant differences in CVD risk factors (SBP, DBP, fasting lipids and glucose) between the two groups (F (10, 59) = 1.6, p = 0.116) as shown in Table 4.10. No differences were observed when the same investigation was carried out in female and male RA patients (See Appendix 7).

Table 4.10 CVD risk factors and global CVD risk scores of unable and able patients.

CVD Risk Factors	Unable (n = 35)	Able (n = 65)	*P*
SBP (mmHg)	145.17 ± 22.78	138.34 ± 19.42	0.196
DBP (mmHg)	82.04 ± 9.05	81.11 ± 11.79	0.738
TC (mmol·l^{-1})	5.12 ± 1.24	5.40 ± 1.15	0.356
TG (mmol·l^{-1})	1.76 ± 0.83	1.41 ± 0.71	0.076
LDL-c (mmol·l^{-1})	2.99 ± 1.11	3.21 ± 1.05	0.417
HDL-c (mmol·l^{-1})	1.31 ± 0.37	1.56 ± 0.45	0.025
Glucose (mmol·l^{-1})	5.58 ± 1.41	5.16 ± 0.77	0.113
Global CVD Risk Score			
Framingham Risk (%)	21.28 ± 12.52	13.99 ± 9.35	0.008
QRISK2 (%)	23.97 ± 13.92	17.64 ± 13.90	0.078

Values are mean ± SD, N = 100. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

However, step ability was associated with Framingham risk score category (low, mod, high risk) (χ^2 (2, n = 100) = 6.47, p = 0.039, phi = 0.27). There was no significant association between step ability and presence of hypertension (medication or high blood pressure) (χ^2 (1, n = 100) = 0.87, p = 0.768, phi = -0.17), dyslipidemia (medication or high cholesterol) (χ^2 (1, n = 100) = 2.26, p = 0.132, phi = 0.05), smoking status (χ^2 (2, n = 100) = 4.25, p = 0.119, phi = 0.21), metabolic syndrome (χ^2 (1, n = 100) = 2.42, p = 0.120, phi = 0.16), number of risk factors (χ^2 (5, n = 100) = 3.43, p = 0.634, phi = 0.19) or family history of heart disease (χ^2 (1, n = 100) = 0.067, p = 0.795, phi = -0.03).

To determine what factors best predict step ability in RA patients a discriminant function analysis was conducted. Predictor variables were selected from each of the above categories (RA related factors, body composition and CVD risk factors). The variables included in the analysis were age, CRP, HAQ, VAS arthritis, waist circumference, BMI, and Framingham CVD risk score. Significant mean differences were observed for all the predictors on the dependent variable except age. While the log determinants were quite similar, Box's M indicated that the assumption of equality of covariance matrices was violated. However, given the large sample size, this problem was not regarded as serious. The discriminate function revealed a significant association between groups and all predictors, accounting for 41.5% of between group variability, although closer analysis of the structure matrix revealed four significant predictors, namely **HAQ** (0.704), **waist circumference** (0.565), **VAS arthritis** (0.548) and **BMI** (0.543). Age and CRP were poor predictors. The cross validated classification showed that overall 80.9% were correctly classified.

4.4 Discussion

This cross sectional study aimed to identify a possible relationship between cardio-respiratory fitness and CVD risk factors, RA disease variables and body composition in a typical RA population attending a routine clinic. One observation of this study was the very low cardio-respiratory fitness levels of RA patients; they had an average predicted fitness of 22 $ml \cdot kg^{-1} \cdot min^{-1}$ as assessed by the step test. This value was similar to that reported by previous RA studies (Minor and Hewett, 1995, Strombeck et al., 2007). However, the primary observation of this study was that despite the poor cardio-respiratory fitness in this current group there was no association with any of the RA disease activity variables, only self reported disability (HAQ) and two of the CVD risk factors, diastolic blood pressure and triglycerides. Cardio-respiratory fitness was however, associated with all measures of body composition with central adiposity (waist circumference) being the greatest predictor of poor cardio-respiratory fitness.

The second striking result of the current study is that 35% of patients were unable to complete the step test; these patients terminated the test before the end of the three minute stage. Despite these RA patients not being able to complete the step test and therefore not allowing an estimation of their cardio-respiratory fitness they have provided some significant findings which will be discussed further in this chapter.

It may seem surprising that cardio-respiratory fitness in the current study failed to correlate with many of the traditional CVD risk factors that have been suggested to exist in previous studies in healthy populations (Carnethon et al., 2003, Gibbons et al., 1983, Sallis et al., 1988). One explanation for lack of association in the current study may be the poor range in cardio-respiratory fitness level in this RA population. Eighty percent of RA patients had a poor cardio-respiratory fitness level. Values above 28 $ml \cdot kg^{-1} \cdot min^{-1}$ represent a good cardio-respiratory fitness level for this age group and one that has been shown to provide a cardio-protective effect (Kodama et al., 2009). However, few RA patients possessed a good cardio-respiratory fitness level and could therefore explain why some expected associations were not observed. Another explanation could be that a third of RA patients were receiving medication to lower CVD risk either by taking anti hypertensive and/or anti hyperlipidemia medication.

Despite few associations between cardio-respiratory fitness and traditional CVD risk factors, cardio-respiratory fitness was strongly associated with body composition. Overall, patients who were less fit had a less favourable body composition. They were heavier, fatter and had a bigger waist and hips. It must be noted however, that this strong association is partly due to measures of body composition (weight) being included in the calculation of cardio-respiratory fitness. However, despite this these results remain consistent with previous findings (Fogelholm et al., 2006, Wong et al., 2004).

In order to determine why some RA patients were unable to complete the step a comparison was made between this group and patients who were able to complete the step test. 'Unable' patients rated their arthritis as worse (VAS arthritis), more painful and disabling (HAQ). Upon examination of the mean scores patients unable to complete the step were on average four years older and inflammation (ESR, CRP) and disease activity (DAS 28) were slightly higher. These differences would also have been significant if the data was analysed using univariate analysis only. However, further analysis was performed to determine the impact of all RA disease variables on step ability. Results showed that HAQ and VAS arthritis were the greatest predictors of step ability. Age, gender, disease duration, disease activity and inflammation did not have a significant impact on the RA patients step ability. This suggests that RA disease itself is not the primary reason that some patients are unable to complete the step test and that it is more likely to be due to patients' perception of their disease and physical ability. It must also be noted that RA patients rated their arthritis (VAS arthritis) and pain whilst in the presence of their rheumatologist/nurse specialist before being approached by the researcher and being asked to complete the step test. A supplementary investigation that does not feature in the main text of this thesis but can be seen in Appendix 8 provides an alternative insight as to why some RA patients experience more physical limitations when RA disease activity is not the primary reason. Ankle brachial pressure index (ABPI), a measure of peripheral vascular disease was also measured in this cross sectional study. The majority (98%) of RA patients had a normal ABPI (> 0.9). However, RA patients unable to complete the step test had a significantly lower ABPI than patients who were able to complete the step test. A lower ABPI was also associated with higher HAQ scores. Perhaps patients who have a lower ABPI, which is not clinically diagnosed as peripheral vascular disease, experience symptoms of a vascular occlusion when performing physical tasks. This is an interesting observation. However, further research and additional clinical investigations are needed to confirm these speculations (see Appendix 8 for further details).

As well as perception of arthritis, physical ability and a lower ABPI, body composition had a major influence on step ability, especially in female RA patients. 'Unable' patients were heavier, fatter, had bigger waists and hips and had a greater prevalence of obesity. Further analysis of body composition variables showed that BMI was the greatest predictor of step ability. Despite the major differences in body composition there was no significant difference in CVD risk factors between 'unable' and 'able' patients. This is not surprising considering there were no differences in the use of anti-hypertensive or anti-hyperlipidemia medication between the two groups. However, 'Unable' patients did have a greater prevalence of having a high Framingham Risk score and high Qrisk2 score (> 20% risk). This could be partially explained by the fact that unable patients were on average four years older but perhaps this could also be due to the accumulated effects of individual risk factors.

Discriminant function analysis confirmed the findings of the study. Patients who rated themselves as having more disability (HAQ), worse arthritis (VAS arthritis), those who had bigger waists and higher BMI were more likely to be unable to complete the step test. Surprisingly, disease activity, inflammation and age did not determine step ability in RA patients. These results verify the detrimental effects of obesity on function and perceived disability that is not explained by RA disease itself. There was no association between physical activity from the IPAQ questionnaire and cardio-respiratory fitness or step ability. Thus patients who were unable to complete the step test did not rate their levels of physical activity any differently to patients who were able to complete the step test. This perhaps highlights the limitations to using such a measure of self reported physical activity (Walsh et al., 2004). This finding is very interesting considering previous studies that have shown physical inactivity in RA, as measured by physical activity questionnaires was associated with a worse cardiovascular risk factor profile (Metsios et al., 2009), older age, obesity, more disability (HAQ), pain, disease activity and fatigue (Sokka and Hakkinen, 2008).

Because RA is associated with increased mortality from CVD caused largely by accelerated atherosclerosis, the main focus of research carried out to date have been on systemic inflammation and its effects (Sattar et al., 2003). Less attention has been focused on the more traditional, modifiable risk factors of CVD because it is believed these risk factors do not sufficiently explain the increased mortality in RA (Del Rincon et al., 2001). Despite this, these risk factors are modifiable and so represent an identifiable target for intervention that should not be ignored (Metsios et al., 2008). The results of the present study support this

statement. When assessing the averages for the total group the individual CVD risk factors do not seem obviously elevated and are very similar to the results reported by Metsios et al. (Metsios et al., 2009). However, when taking into consideration patients who were receiving anti-hypertensive treatment and those with a high blood pressure at the time of assessment a very large percentage of patients were hypertensive (66%). The prevalence of hypertension observed in this study is very similar to that reported by Panoulas et al. (Panoulas et al., 2007) who found that 70.5% of RA patients were hypertensive. These results suggest that the prevalence of hypertension observed in RA patients is significantly higher than that reported for the general population in which 48% of adults aged between 55-64 years are believed to be hypertensive (HSE, 2010). In the present study there was a similar trend for patients with dyslipidemia (69%). These results show that in the current study 34% of patients were not being treated for hypertension while 41% of patients were not being treated for having abnormal lipids. Another important finding is that 41% of patients were classified as having metabolic syndrome. Uncontrolled blood pressure, dyslipidemia, metabolic syndrome along with poor cardio-respiratory fitness, physical inactivity and the level of obesity highlights the importance of these risk factors. It also suggests that the EULAR message about careful screening for and the management of CVD risk factors in RA is generally being overlooked (Peters et al., 2010), as the rate of potential underdiagnosed hypertension and dyslipidemia remains very high in the current and other RA populations (Panoulas et al., 2007).

Cardiovascular co-morbidity and mortality are increased in RA (Bacon and Townend, 2001). Although not assessing cardiovascular events the results of the present study do highlight that the level of poor cardio-respiratory fitness, high physical inactivity, and obesity are a cause for concern in this population. All of these measures are risk factors for CVD in their own right but more importantly they are modifiable. Obesity seems to have a considerable impact on how RA patients, especially females, rate their disability and the severity of their arthritis, which is not fully explained by markers of inflammation or disease activity. The impact of obesity in the current RA group is discussed further in the next chapter.

The strengths and weaknesses of this study warrant comment. The cross sectional nature of this study means that no conclusions can be made on the potential cause and effect of cardio-respiratory fitness, CVD risk factors and the future cardiovascular health of RA patients. Because all measures are assessed at one time point this study can determine prevalence of disease (e.g. hypertension), however, this can also result in overestimation. Despite

limitations to cross sectional studies, this investigation benefits from a large sample size, in which participants were selected at random within a real life clinical setting. Thus, the results of the present study are likely representative of the general RA population.

4.5 Conclusion

Overall the current RA patients had very poor cardio-respiratory fitness that was below average when compared to the general population. This poor cardio-respiratory fitness was not associated with rheumatoid disease or traditional CVD risk factors in general. However, body composition was a major determinant. Reported measures of worse arthritis, pain and self reported disability (HAQ) prevented one third of RA patients from completing the step test, not the disease itself. It is important to note that all of these major contributing factors to step ability were subjective measures. Patients unable to complete the step test, in particular the female RA patients, also had significantly worse body composition, they were heavier, fatter, had bigger waists and hips and a greater prevalence of obesity. BMI, waist and weight seemed to have the greatest influence of all body composition variables on determining step ability. Being unfit and the level of obesity observed in this RA population warrants consideration as a risk factor, distinctly from inactivity, and worthy of screening and intervention. Thus, the level of obesity observed and its impact on patients with RA requires further analysis. This is discussed in length in Chapter 5.

5 Chapter 5:

Impact of obesity on patients with rheumatoid arthritis

5.1 Introduction

Like poor cardio-respiratory fitness, obesity is also an independent risk factor for CVD (Lavie et al., 2009), yet very few studies have directed their focus on obesity in the RA population. Body weight is often routinely assessed when RA patients attend rheumatology clinics. However, this is mainly used as a demographic characteristic reported in medical notes and is generally excluded from further interpretation (Stavropoulos-Kalinoglou et al., 2011). Obesity seems to have a major impact on how RA patients perceive their arthritis and their physical function which was evident from the findings of Chapter 4. The aim of the current chapter was to investigate the association between measures of obesity and RA disease related factors and CVD risk factors and to establish any differences in RA patients who had a normal BMI, were overweight or obese.

5.2 Methods

5.2.1 Protocol

The same 100 RA patients investigated in Chapter 4 were studied in order to determine the impact of obesity in these patients. A full description of the methodology used has been given in Chapters 2 and 4.

5.2.2 Statistical Analysis

Pearson's correlation coefficient (parametric), Spearman's correlation coefficient (non parametric) and logistic regression were used to assess the association between measures of obesity (BMI, body fat percent and central adiposity) and RA disease factors and CVD risk factors and associated variables. The group of 100 RA patients were also split according to their BMI – normal (BMI < 25 $kg \cdot m^{-2}$), overweight (BMI 25 – 29.9 $kg \cdot m^{-2}$) and obese (BMI > 30 $kg \cdot m^{-2}$) (WHO, 2000). MANOVA was used to assess the differences between these BMI groups for RA disease variables and CVD risk factors. If MANOVA revealed a significant difference the dependent variables were considered separately using a Boneferroni adjusted alpha level (0.05/number of dependent variables). Where necessary post–hoc comparisons using the Tukey HSD test was performed. Chi squared analysis was used to assess the association between BMI groups and all other categorical variables – RA disease, CVD risk and physical activity. Statistical significance was set at $p < 0.05$ for all analyses unless stated otherwise.

5.3 Results

100 RA patients (69% female) were included in this investigation and were categorised based on their individual BMI: normal BMI group (27 female, 12 male; mean ± SD age, 60.4 ± 10.7 years), overweight group (21 female, 13 male; age, 59.2 ± 10.4 years) and obese group (21 female, 6 male; age, 59.2 ± 9.3 years). The body composition of these RA patient groups are outlined in detail in Table 5.1. Individual measures of obesity worsened significantly with increasing BMI (F (12, 182) = 17.45, p = 0.000; Wilks' Lambda = 0.216; partial eta squared = 0.53). Obese patients were on average 20 kg heavier and 20% fatter than the normal BMI group, even when considering that the obese patients were predominantly female.

Table 5.1 Body composition of the BMI groups.

Body Composition	Normal (n = 39)	Overweight (n = 34)	Obese (n = 27)	*P*
Weight (kg)	62.63 ± 9.16	72.92 ± 9.24	92.96 ± 12.28	0.000*
BMI ($kg \cdot m^{-2}$)	23.01 ± 2.48	27.57 ± 1.40	34.93 ± 4.24	0.000*
Body Fat (%)	29.03 ±10.84	36.06 ± 9.14	52.27 ± 14.11	0.000*
Waist (cm)	81.15 ± 9.02	92.12 ± 8.48	103.54 ± 9.73	0.000*
Hip (cm)	93.04 ± 7.03	98.74 ± 5.79	113.18 ± 7.99	0.000*
Waist:Hip	0.87 ± 0.06	0.93 ± 0.07	.91 ± .07	0.001#

Values are mean ± SD, N = 100. *Significant difference between all 3 groups, #significant difference between normal and the other two groups using a Boneferroni adjusted alpha level of $P < 0.008$, BMI; body mass index.

A higher BMI was associated with less favourable subjective markers of RA disease, as per Chapter 4. Patients with a higher BMI reported worse arthritis (VAS arthritis), more pain and more disability (HAQ) than patients in the normal BMI category. There was no association between BMI and disease duration, inflammation or disease activity ($p > 0.05$). Similar results were obtained for body fat percent. However, central adiposity which was determined by waist circumference was also associated with CRP. This implies that accumulation of fat around the trunk is associated with higher levels of inflammation (CRP), see Table 5.2. BMI, body fat percent and waist circumference were positively associated with triglycerides. With only BMI and waist circumference also being associated with HDL-c, see Table 5.3. Body composition did not correlate with any of the CVD global risk scores, see Table 5.4. However, there was a significant association between BMI and metabolic syndrome (OR = 1.15, 95% CI = 1.05-1.25; p = 0.002), central adiposity and metabolic syndrome (OR = 1.08, 95% CI = 1.03-1.12; p = 0.000), but not for body fat percent and metabolic syndrome (OR = 1.02, 95% CI = 1.00-1.05; p = 0.078).

Table 5.2 Associations between body composition indices (BMI, body fat percent and waist circumference) and RA disease variables.

	Disease Duration	ESR	CRP	Tender Joints	Swollen Joints	DAS 28 ESR	DAS 28 CRP	VAS arthritis	Pain	HAQ
BMI	0.121	0.009	0.155	0.042	-0.07	0.129	0.103	0.237*	0.349**	0.273**
Body Fat %	0.141	-0.124	-0.067	0.042	-0.101	0.067	0.067	0.178	0.281**	0.221*
Waist	0.121	0.053	0.270**	0.095	-0.088	0.152	0.143	0.224*	0.286**	0.226*

Values are Pearson's or Spearman's correlation's, N = 100.*P < 0.05, **P < 0.01, BMI; body mass index, ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

Table 5.3 Associations between body composition indices (BMI, body fat percent and waist circumference) and CVD risk factors.

	SBP	DBP	TC	TG	LDL-c	HDL-c	Glucose
BMI	0.086	-0.058	-0.042	0.299**	-0.039	-0.258*	0.168
Body Fat %	-0.045	-0.102	0.135	0.360**	0.08	-0.125	0.056
Waist	0.07	-0.038	-0.083	0.319**	-0.073	-0.304**	0.162

Values are Pearson's or Spearman's correlation's, N = 100. *P < 0.05, **P < 0.01, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

Table 5.4 Associations between body composition indices (BMI, body fat percent and waist circumference) and CVD global risk.

	Framingham CVD Risk	QRISK2 CVD Risk
BMI	0.098	0.06
Body Fat %	-0.026	-0.097
Waist	0.084	0.111

Values are Pearson's correlation's, N = 100.BMI; body mass index.

5.3.1 RA Factors

There was no significant difference in RA disease related factors (age, disease duration, inflammation, disease activity, pain, HAQ) between the three BMI groups (F (22, 170) = 1.15, p = 0.299). Reported pain and disability (HAQ) mean scores were higher in the obese patients than that of overweight or normal weight patients (see Table 5.5).

Table 5.5 RA related factors of the BMI groups.

RA Characteristic	Normal (n = 39)	Overweight (n = 34)	Obese (n = 27)	*P*
Age (years)	60.44 ± 10.65	59.24 ± 10.44	59.23 ± 9.30	0.852
Disease duration (years)	10.58 ± 9.02	9.05 ± 7.01	11.69 ± 11.66	0.541
ESR ($mm \cdot hr^{-1}$)	16.92 ± 14.76	15.27 ± 12.14	16.58 ± 10.58	0.856
CRP ($mg \cdot l^{-1}$)	14.79 ± 24.01	10.79 ± 15.42	9.85 ± 8.25	0.490
Tender joints (n)	1.74 ± 3.63	2.30 ± 5.15	2.15 ± 3.38	0.839
Swollen joints (n)	1.08 ± 2.62	0.63 ± 1.88	0.38 ± 1.17	0.395
VAS arthritis (0-100)	25.89 ± 21.10	35.30 ± 26.19	36.35 ± 24.00	0.134
Pain (0-100)	**15.15 ± 22.95**	**21.15 ± 25.65**	**36.73 ± 32.05**	**0.007**
DAS 28 ESR	2.61 ± 1.47	2.74 ± 1.46	2.92 ± 1.24	0.677
DAS 28 CRP	2.67 ± 1.19	2.80 ± 1.21	2.86 ± 1.05	0.793
HAQ (0-3)	**0.65 ± 0.67**	**0.90 ± 0.70**	**1.18 ± 0.88**	**0.022**

Values are mean ± SD, N = 100. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

BMI category was not associated with gender (χ^2 (2, n = 100) = 1.81, p = 0.405, phi = 0.13), DMARD group (χ^2 (4, n = 100) = 0.21, p = 0.995, phi = 0.05) or steroid exposure (χ^2 (2, n = 100) = 2.53, p = 0.282, phi = 0.16).

5.3.2 CVD Risk Factors and Global CVD Risk Scores

There was no difference in CVD risk factors or global CVD risk scores (blood pressure, fasting lipids, glucose, Framingham risk score or QRISK2) between the three groups, when controlling for gender (F (18, 116) = 0.79, p = 0.704) (see Table 5.6).

Table 5.6 CVD risk factors and Global CVD risk scores of the BMI groups

CVD Risk Factors	Normal (n = 39)	Overweight (n = 34)	Obese (n = 27)	*P*
SBP (mmHg)	135.50 ± 19.47	141.87 ± 19.91	141.76 ± 23.57	0.806
DBP (mmHg)	80.27 ± 11.23	80.83 ± 9.27	83.48 ± 12.32	0.648
TC ($mmol \cdot l^{-1}$)	5.43 ± 1.28	5.03 ± 0.98	5.45 ± 1.24	0.402
TG ($mmol \cdot l^{-1}$)	1.34 ± 0.67	1.49 ± 0.62	1.80 ± 0.94	0.083
LDL-c ($mmol \cdot l^{-1}$)	3.28 ± 1.09	2.94 ± 0.91	3.17 ± 1.19	0.503
HDL-c ($mmol \cdot l^{-1}$)	1.56 ± 0.50	1.39 ± 0.34	1.46 ± 0.44	0.393
Glucose ($mmol \cdot l^{-1}$)	5.27 ± 1.08	5.19 ± 0.76	5.47 ± 1.04	0.514
Current smoker (n)	11	8	4	-----
Global CVD Risk Scores				
Framingham risk (percent)	16.38 ± 11.65	15.36 ± 8.95	16.00 ± 10.49	0.596
QRISK2 (percent)	20.43 ± 14.61	19.27 ± 13.38	19.70 ± 12.48	0.706
Metabolic syndrome (n)	10	16	15	-----

Values are mean ± SD, N = 100. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

As shown in Table 5.6 the prevalence of metabolic syndrome increased with increasing BMI and thus BMI category was significantly associated with metabolic syndrome (χ^2 (2, n = 100) = 6.68, p = 0.035, phi = 0.26). However, there was no association between BMI category and smoking status (χ^2 (4, n = 100) = 6.34, p = 0.175, phi = 0.25), dyslipidemia (on medication or abnormal lipids) (χ^2 (2, n = 100) = 1.93, p = 0.382, phi = 0.14) or hypertension (on medication or high blood pressure) (χ^2 (2, n = 100) = 2.29, p = 0.319, phi = 0.15), family history of heart disease (χ^2 (2, n = 100) = 0.51, p = 0.777, phi = 0.07) or number of CVD risk factors (χ^2 (2, n = 100) = 0.51, p = 0.777, phi = 0.71).

5.3.3 Cardio-respiratory Fitness and "Step Ability"

There was no difference in cardio-respiratory fitness between the three BMI groups (p = 0.177). Measured cardio-respiratory fitness for normal, overweight and obese RA patients was 22.9 ± 6.4 $ml \cdot kg^{-1} \cdot min^{-1}$, 22.1 ± 6.1 $ml \cdot kg^{-1} \cdot min^{-1}$ and 19.13 ± 2.8 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively (see Figure 5.1).

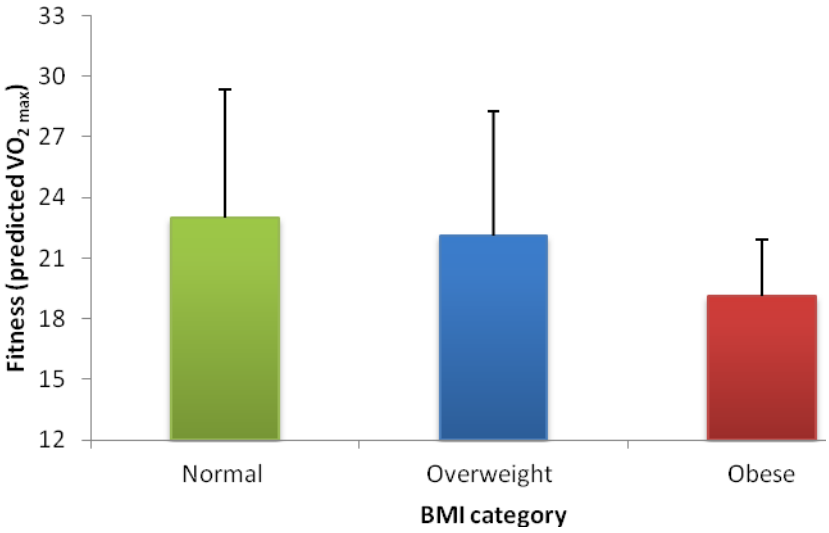

Figure 5.1 Fitness level of the BMI groups, Values are mean ± SD, N = 65.

There was however, a significant association between BMI category and step ability group (χ^2 (2, n = 100) = 10.69, p = 0.005, phi = 0.33). The majority of RA patients who were obese were unable to complete the step, whereas the majority of RA patients with a normal BMI were able to complete the step test (Figure 5.2).

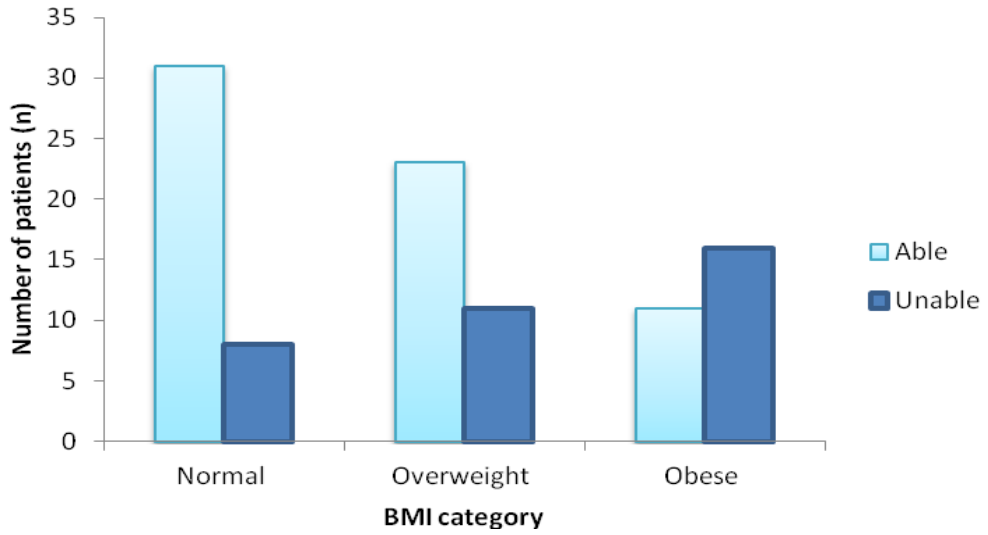

Figure 5.2 BMI category of RA patients 'able' and 'unable' to complete the step, N = 100.

There was no association between BMI category and physical activity category (χ^2 (4, n = 100) = 2.09, p = 0.719, phi = 0.15) (Figure 5.3). MET min·week^{-1} for the three BMI groups were as follows: normal (1633 ± 2666 MET min·week^{-1}), overweight (1119 ± 1680 MET min·week^{-1}) and obese (1214 ± 2639 MET min·week^{-1}). There was no difference in reported MET min·week^{-1} between the three BMI groups (p = 0.617).

5.3.4 Physical Activity

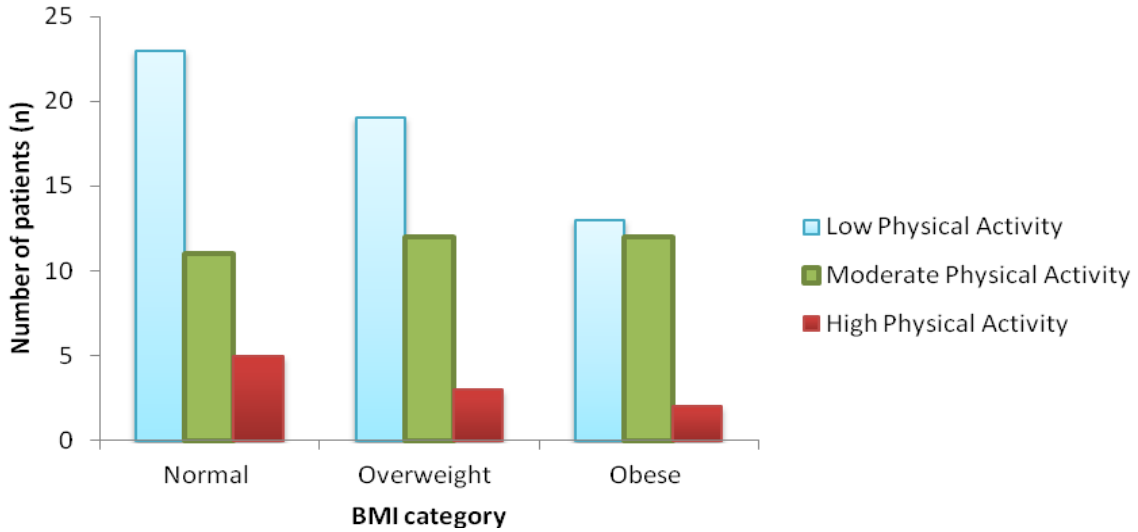

Figure 5.3 Reported physical activity and BMI category of RA patients, N = 100.

5.4 Discussion

This is the first study of its kind to include a measurement of cardio-respiratory fitness when examining the impact obesity has on RA patients. In the present study it was observed that a less favourable body composition was associated with worse arthritis, more pain and more disability. CRP was also elevated in RA patients who had a bigger waist circumference. When examining the differences between the BMI groups, RA patients that were obese tended to report more pain and disability compared to their normal weight counterparts. However, body composition was not associated with disease duration, inflammation or disease activity and these were not significantly different when examining the three BMI groups. Body composition was however, associated with high levels of triglycerides, low HDL-c and presence of metabolic syndrome but not with other CVD risk factors, or global CVD risk scores.

As expected from the results of the previous chapter (Chapter 4), RA patients who were obese were less likely to complete the step test. The purpose of the separate analyses presented in this chapter was to determine whether patients to complete the step test were limited by disease and/or body composition factors. The current analysis found that greater adiposity was associated with worse reported arthritis, more pain and more disability. Disease duration, ESR and disease activity were not significantly associated with body composition and did not differ between the three BMI groups. However, on this occasion central adiposity measured by waist circumference was associated with higher levels of CRP. This association helps to answer the above question and suggests that the inflammation (CRP) observed in this RA population is elevated because of excess adiposity and not necessarily because of increased disease activity (Festa et al., 2001). This finding is supported by Santos et al. (2005) who found that central obesity was a major contributing feature of high CRP and metabolic syndrome (Santos et al., 2005). A study by Fontana et al. (2007) helps explain this link; this group of researchers examined abdominal visceral fat by sampling blood from the hepatic portal vein of obese patients undergoing gastric bypass surgery. They found that abdominal visceral fat was secreting very high levels of interleukin-6 (IL-6) into portal vein blood. This increased level of IL-6 was in turn strongly correlated with increased levels of CRP (Fontana et al., 2007).

Body composition was also found to be associated with some measures of CVD risk in the present study. More specifically, a higher BMI and greater central adiposity were significantly associated with higher triglycerides and lower HDL-c. Similar associations were observed in women with the metabolic syndrome (Pimentel et al., 2010). Interestingly, despite these associations between markers of obesity and some CVD risk factors, there was no difference found in the other traditional CVD risk factors or global CVD risk scores between the three BMI groups in the current study. Obese patients did however have an increased prevalence of the metabolic syndrome, which is an established risk factor for CVD (Galassi et al., 2006). The obvious explanation for this is that both triglycerides and HDL-c are included in the criteria for the determination of metabolic syndrome and so it is unsurprising that BMI is associated with these specific CVD variables and not others such as total cholesterol or LDL-c. These results are very interesting as one would expect RA patients who are also obese to have a significantly worse CVD risk profile as suggested by Stavropoulos-Kalinoglou et al. (2009) who previously investigated the association between obesity and modifiable risk factors of CVD. They found a near linear relationship between BMI and CVD risk factors and when examining the differences in BMI subgroups, they found that patients who were obese also had a higher CVD risk. They also reported that RA patients who were obese were more likely to fulfil criteria for the metabolic syndrome, a finding also supported by the current investigation. However, it must be noted that the findings reported by Stavropoulos-Kalinoglou et al. (2009) were based on their revised RA specific BMI groups in which they suggest BMI should be lowered by 2 $kg \cdot m^{-2}$ and not the well known BMI cut offs used in the current thesis (Stavropoulos-Kalinoglou et al., 2009). One could argue therefore, that the lack of differences observed between the three BMI groups in the current study was explained by the inability of the standard BMI to correctly identify obesity in RA patients. However, the analysis performed using the standard BMI in this chapter were repeated using the results for body fat percent ($F(18,116) = 1.08$, $p = 0.386$) and the revised BMI cut offs ($F(18,116) = 1.20$, $p = 0.274$) suggested by Stavropoulos-Kalinoglou et al. (2009), both of which provided very similar results (see Appendix 9 for further details).

Another explanation for the lack of differences in CVD risk factors between the BMI groups could be that obesity has a protective effect against CVD in RA. Escalante et al. (2005) suggested that BMI had a paradoxical effect on CVD mortality in RA. They observed lower mortality rates amongst the heavier patients. However, they did suggest that this protective

effect was modified by systemic inflammation. They believed that when ESR was low, BMI had a protective effect, but when ESR was high this protective effect diminished (Escalante et al., 2005). The values for ESR reported in that study were much higher than that observed in the current investigation and indeed throughout this thesis. Unfortunately, Escalante et al. (2005) did not report any values for individual CVD risk factors and therefore more solid comparisons cannot be made. Perhaps the low levels of inflammation (ESR) observed in this RA population is having a beneficial effect on their overall cardiovascular risk factor profile.

Although poor cardio-respiratory fitness was strongly associated with a less favourable body composition as shown in Chapter 4, there was no significant difference in cardio-respiratory fitness levels between the three BMI groups. Although not significant, normal weight patients did have a higher cardio-respiratory fitness level when compared to their overweight and obese counterparts. However, this data needs to be considered alongside the data for step ability. Obese patients were less likely to able to complete the step test (Figure 5.4) and therefore one could speculate that that their cardio-respiratory fitness level would have been much less than those who were able to complete the step test. Despite the majority of obese RA patients not being able to complete the step test, reporting more pain and disability; there was no difference in their reported physical activity. Obese patients reported the same level of physical activity per week as their normal weight counterparts. Perhaps, this finding highlights the subjective nature of assessing physical activity using a questionnaire like the IPAQ. Previous research has suggested that the IPAQ in particular can overestimate physical activity, especially moderate physical activity (Craig et al., 2003). One study reported an overestimation of 247% using the IPAQ when compared to physical activity measured by an accelerometer (Johnson-Kozlow et al., 2006). One of the main reasons for this discrepancy has been attributed to social desirability (Vanhees et al., 2005). "Social desirability" has been explained as a defensive tendency of individuals to portray themselves in keeping with perceived cultural norms. It has also been suggested that people, especially women are more likely to underreport their fat, total energy intake and overestimate their level of physical activity (Adams et al., 2005, Hebert et al., 2002). With RA being a chronic disease that is more common in women, perhaps the use of self reported physical activity questionnaires should be kept to a minimum and the measurement of cardio-respiratory fitness should be performed instead.

5.5 Conclusion

Assessing the impact of obesity on RA disease, CVD risk factor profile and cardio-respiratory fitness and function has provided some novel findings. This study, the first of its kind, has shown that obesity heavily impacts on patients' perception of their disease and physical ability. It is strongly associated with the metabolic syndrome and its individual components (TG, HDL-c) but not with the other traditional CVD risk factors as one might expect. One of the most striking findings of this study is that obesity is the main reason some patients are unable to complete the step and not their RA disease. Now that some key modifiable CVD risk factors have been highlighted including poor cardio-respiratory fitness and obesity, the next chapter describes an exercise intervention designed to improve upon these.

6 Chapter 6:

Can a short term supervised exercise intervention improve RA patients overall cardiovascular health and general well being?

6.1 Introduction

Regular exercise and being physically active provides a multitude of health benefits for the general population and patients with chronic diseases, especially individuals with RA (discussed in detail in Chapter 1). Despite this knowledge, the majority of RA patients remain physically inactive (Sokka et al., 2008). This extreme physical inactivity plays an important role in terms of patient health and disease progression. It also highlights the need to encourage exercise amongst this population as part of routine care.

Benefits of exercise in RA patients include improved cardio-respiratory fitness (Stenstrom and Minor, 2003), increased muscle mass (Lemmey et al., 2009), reduced adiposity (Walsmith and Roubenoff, 2002) and improved muscle strength and physical functioning (Hakkinen, 2004). It is important to note that these exercise benefits are all achieved without exacerbation of disease activity or joint damage (Van den Ende et al., 2000).

Since RA is associated with increased morbidity and mortality from cardiovascular disease (CVD) a goal of any RA treatment regime should be to reduce cardiovascular co-morbidity, in line with the overall aim of prolonging and improving quality of life (QoL). Poor cardio-respiratory fitness is strongly associated with cardiovascular mortality in apparently healthy men and women, those with co-morbid conditions (hypertension, obesity, diabetes mellitus type 2) and those with known coronary artery disease (Franklin and McCullough, 2009). With cardiovascular mortality accounting for more than 50% of deaths in the RA population (Wolfe et al., 1994), it is unsurprising that individuals with this chronic illness have cardio-respiratory fitness levels 20-30% lower than age matched healthy controls (Häkkinen et al., 2001) and patients who are generally physically inactive have been shown to have a significantly worse

cardiovascular risk factor profile (Metsios et al., 2009) in particular poor cardio-respiratory fitness and obesity (chapter 4).

Exercise training can reduce mortality by 20-30% (Taylor et al., 2004). Thus, the probable cardio-protective benefit of exercise to patients with RA cannot be ignored. To date, most studies have focused on the improvements in functional ability and other RA related disease outcomes. A recent Cochrane review highlighted evidence for a positive effect of short term exercise on aerobic capacity (Hurkmans et al., 2009). It is worth noting that of the 8 studies included in this review, not one reported any cardiovascular risk factors. A more recent systematic review and meta-analysis of randomised controlled trials also showed that aerobic exercise improves important RA patient outcomes such as function, QoL and pain (Baillet et al., 2010). Again, the effect of exercise on cardiovascular risk factors was not included in these investigations. With a clear gap in research devoted to CVD and exercise in RA, the need for research investigating the effect of exercise training on cardio-respiratory fitness and CVD risk factors in RA is paramount.

6.1.1 What Exercise Interventions Have Been Done?

The beneficial effect of exercise on CVD risk factors in RA remains to be investigated. In order to plan an appropriate exercise intervention, a literature search of exercise interventions in other clinical populations (e.g. diabetes mellitus, hypertensive patients, obesity) was undertaken. Although many of these studies investigated long term interventions, the primary focus of the study described here was the beneficial effects of short term exercise interventions (see Table 6.1). From these exercise interventions it was evident that improvements in fitness and overall cardiovascular health could be achieved by exercising at least 3 times per week for 8-12 weeks.

It was hypothesised that 8 weeks of supervised aerobic exercise designed to increase RA patients cardio-respiratory fitness would also improve their cardiovascular risk factors, body composition and symptoms of RA disease.

Table 6.1 Short term exercise interventions in various non-RA clinical populations.

Author (date)	Population	Exercise	Duration	Frequency	Outcome
Yu et al. (2003)	Obese with CHD, Age 62 yrs	Aerobic 65-80% MHR (1 hour)	8 weeks	2 sessions/wk	Improved fitness, HDL-c, LDL-c, WHR
Lazarevic et al. (2006)	Type 2 diabetes, Age 54 yrs	Brisk walking 50-75% MHR	12 weeks	3 -5 sessions/wk	Improved SBP, DBP
Walker et al. (1999)	Diabetes & normoglycemic Age 58 years	Walking self paced (1 hour)	12 weeks	5 sessions/wk	Improved VO_2, weight, BMI, glucose, LDL-c, TG
Maiorana et al. (2002)	Type 2 diabetes, Age 52 yrs (excluded – TC > 6, BP > 160)	Circuit training (aerobic and resistance) 1 hour	8 weeks	3 sessions/wk	Improved glucose, resting HR, WHR, fat percent, muscle strength, VO2
Kelemen et al. (1990)	Hypertensive men, Age 47 yrs	30 min weight training, 20 mins aerobic, 14 – 16 RPE	10 weeks (reported differences after 7 weeks)	3 sessions/wk	Improved SBP, DBP, TC, LDL-c, HDL-c, Fitness (15%), weight
Yeater et al. (1990)	Type 2 diabetes, Age 56 yrs	Walking/slow jogging (40–45 mins)	8 weeks	3 sessions/wk	Improved fitness, SBP, resting HR, TG

CHD; coronary heart disease, TC; total cholesterol, TG; triglycerides, HDL-c; high density lipoprotein, LDL-c; low density lipoprotein, WHR; waist hip ratio, SBP; systolic blood pressure, DBP; diastolic blood pressure, VO_2; oxygen consumption, BMI; body mass index, MHR; maximum heart rate, RPE; ratings of perceived exertion.

6.2 Methods

6.2.1 Power Calculation

To determine the sample size, an online power calculator was used (DSS Research, beta error level of 20%) utilizing data from similar exercise interventions carried out in other clinical populations (see Table 6.1), mainly type 2 diabetes (Lazarevic et al., 2006), obesity (Yu et al., 2003) and hypertension (Kelemen et al., 1990). The power calculation was based on a variety of cardiovascular risk factors - systolic blood pressure, diastolic blood pressure, cardio-respiratory fitness and high density lipoprotein. These risk factors were chosen because their baseline mean values were similar to the mean values reported in the 100 RA patients that were tested in Chapter 4. The power calculations based on the above risk factors calculated a sample size ranging from N = 5 to N = 14.

6.2.2 Participant Recruitment

With ethical approval (REC reference: 11/WA/0206), thirteen RA patients were recruited into the study. Of these 10 patients completed the 8 week exercise programme. All patients recruited had a diagnosis of RA (Arnett et al., 1988). The remaining three RA patients were classed as drop outs for the following reasons: moved away from the area, called for surgery, decided not to participate after the initial assessment.

6.2.3 Protocol for Baseline and Post Intervention Assessment

Participation in this study comprised of three parts – baseline assessment (pre test), the 8 week exercise training programme and the post intervention assessment (post test). The measures assessed at baseline and post intervention are outlined below (full details are provided in Chapter 2). Measures that have only been used in the current chapter are described in detail. Details of the exercise programme are given in Table 6.2.

Cardio-respiratory Fitness and Function

Cardio-respiratory fitness was measured using the Siconolfi step test. Previously, we have shown that this simple test provides a valid and reliable estimation of $VO_{2\ max}$ (Chapter 3), in patients with RA. Briefly, the test involves stepping up and down a portable 10 inch step for 3 minutes at a rate of 17 steps per minute. Heart rate was measured using a heart rate monitor and recorded at the end of the three minute stage (see Chapter 2 for a detailed description). Physical function was measured objectively using the 8 foot 'Up and Go' and 30 second sit-to-stand test.

30 second Sit to Stand

The 30 second sit to stand test is a measure of lower body strength. It gives an indication of an individual's ability for numerous tasks such as climbing stairs, walking and getting out of a chair, bathtub or car (Jones and Rikli, 2002). The procedure for the test is as follows: the participant is seated with their feet shoulder width apart, flat on the floor. Arms must be crossed at the wrists and held close to the chest. From the sitting position, the participant stands completely up, then completely back down, and this is repeated for 30 seconds. Up and down equals one chair stand. If the participant has completed a full stand from the sitting position when the time is elapsed, the final stand is counted in the total. Recommended ranges for this test based on gender and age group are shown in Table 1-2 (Appendix 7), values are taken from (Jones and Rikli, 2002).

8 foot Up and Go

The 8 foot up and go test is a measure of agility, speed and balance whilst moving (Jones and Rikli, 2002). This test is performed with the participant seated, hands resting on the knees and feet flat on the floor. The participant is timed as they stand up from a seated position; walk as quickly as possible around a cone 8 feet away from the chair, and return to a seated position. Recommended ranges for this test based on gender and age group are shown in Tables 3-4 (Appendix 7), with values taken from (Jones and Rikli, 2002).

Blood pressure and Fasting Lipids, Glucose

After ten minutes of rest in the seated position, blood pressure was measured in duplicate using the auscultatory method. Each participant was required to provide a fasting blood sample within 1 week of this testing session to assess concentrations of lipids and glucose in the blood plasma.

Body Composition

Height and body mass were measured by standard procedures and body mass index (BMI) was calculated ($kg \cdot m^{-2}$). Percentage body fat was measured using bioelectrical impedance analysis (Tanita corp., Tokyo, Japan). Waist and hip circumference was also measured to determine waist hip ratio (waist: hip).

RA Disease and Related Factors

Patients were asked to fill in questionnaires regarding their activities of daily living (Health Assessment Questionnaire), Quality of Life (SF-36) and fatigue (MAF). Patients were asked to rate their arthritis (global health) and current pain using a 10 cm visual analogue scale (VAS). An exercise physiologist examined the number of tender and swollen joints to determine disease activity (DAS 28). Patients were also required to have a routine blood test to assess level of inflammation (ESR and CRP) within one week of the testing session.

Quality of Life

The SF-36 Health Survey (Ware, 2000) is a questionnaire that measures eight different health concepts:

1. Physical functioning
2. Role limitations because of physical health problems
3. Bodily pain
4. Social functioning
5. General mental health (psychological distress and psychological wellbeing)

6. Role limitations because of emotional problems
7. Vitality (energy/fatigue)
8. General health perceptions

The SF-36 can also be divided into two aggregate summary measures - the physical component summary and the mental component summary. The SF-36 has been administered successfully in general population surveys all over the world (Ware et al., 1995). It has been used in young people, older adults and patients with chronic diseases (McHorney et al., 1994, Ware et al., 1993). The questionnaire is regarded as a very useful measure of health status which can be administered in 5-10 minutes with a high degree of acceptability and data quality (Ware et al., 1993). A copy of the SF-36 health survey can be seen in Appendix 8.

Fatigue

The Multidimensional Assessment of Fatigue (MAF) questionnaire was originally developed to evaluate self-reported fatigue in patients with RA (Belza, 1995). The MAF is a 16 item scale that measures fatigue according to four dimensions: degree and severity, distress that it causes, timing of fatigue (over the past week, when it occurred and any changes), and its impact on various activities of daily living (household chores, cooking, bathing, dressing, working, socializing, sexual activity, leisure and recreation, shopping, walking, and exercising). MAF scores range from 1 (no fatigue) to 50 (severe fatigue). This questionnaire has been shown to be reasonably valid and reliable and sensitive to change (Neuberger, 2003). A copy of this questionnaire can be seen in Appendix 9.

6.2.4 Exercise Training

After baseline assessment participants trained 3 times a week for 8 weeks at the physiotherapy gym, Ysbyty Gwynedd. All exercise sessions were supervised by an exercise physiologist (myself). Each exercise training session lasted 60 minutes and consisted of three ten minute aerobic exercises with a short rest in between each one. Participants chose the exercise and the order in which they were completed (treadmill, bike, rower, stepper, cross trainer). Exercise intensity was increased from 55%-85% predicted heart rate maximum (220-age) during the 8 week programme and included both continuous and interval training patterns (see Table 6.2). Heart rate and ratings of perceived exertion (RPE scale) were monitored individually throughout the exercise session. After the aerobic exercise all participants completed resistance training exercises (calf raises, leg raises, knee raises, squats and abdominal curls). Participants completed 15 repetitions (reps) and 2 sets of each exercise at week 1 and this was progressed to 15 reps, 10 pulses (fast repetitions) and 3 sets at week 8. An example of how much performance increased over the 8 weeks can be seen in Table 6.3.

Table 6.2 Exercise intensity progression from week 1 to week 8

	Warm up	Exercise 1	Exercise 2	Exercise 3
Week 1	5 min 50% HRM	55% HRM	55% HRM	55% HRM
Week 2	5 min 50% HRM	55% HRM	65% HRM (2 min) 55% HRM (3 min)	55% HRM
Week 3	5 min 50% HRM	60% HRM	65% HRM (3 min) 55% HRM (2 min)	60% HRM
Week 4	5 min 55% HRM	70% HRM (2 min) 60% HRM (3 min)	65% HRM	70% HRM (2 min) 60% HRM (3 min)
Week 5	5 min 55% HRM	70% HRM	80% HRM (3 min) 65% HRM (2 min)	70% HRM
Week 6	5 min 60% HRM	70% HRM	80% HRM (3 min) 65% HRM (2 min)	70% HRM
Week 7	5 min 60% HRM	80% HRM (3 min) 65% HRM (2 min)	75% HRM	80% HRM (3 min) 65% HRM (2 min)
Week 8	5 min 60% HRM	85% HRM (3 min) 60% HRM (2 min)	85% HRM (3 min) 60% HRM (2 min)	85% HRM (3 min) 60% HRM (2 min)

HRM; heart rate maximum

Table 6.3 Example of maximum performance increase from week 1 to week 8 on each of the aerobic exercise machines. Results are from a selection of participants.

Machine	Week 1	Week 8	Performance Increase (%)
Treadmill	0.64 miles	1.08 miles	69%
Cross Trainer	1.51 km	2.2 km	46%
Rower	750 m	1530 m	104%
Stepper	29 floors	50 floors	72%
Bike	0.8 miles	1.5 miles	88%

km; kilometres, m; metres.

6.2.5 Statistical Analysis

Data was analyzed using the Statistical Package for the Social Sciences, version 19 (SPSS, Chicago, IL, USA). Dependent t-test analysis was used to determine significant differences between pre and post test measures. The effect size was calculated using eta squared ($t^2 \div t^2 + (N-1)$). Significance level was set at $p < 0.05$ for all analyses.

6.3 Results

Ten patients (8 female; age range 54-71 years) with established RA completed 8 weeks of group exercise. Patient characteristics are displayed in Table 6.4.

Table 6.4 RA patient baseline characteristics

Characteristic	Mean/%	SD
Age (years)	64.2	5.9
Disease duration (years)	10.7	11.5
RF positive	70%	
CCP positive	60%	
CRP < 5 $mg \cdot l^{-1}$	100%	
DAS 28 < 2.6	60%	
Current DMARDS		
MTX	80%	
SSZ	10%	
Hydroxychloroquine	10%	
Humira	20%	
Current steroid		
Prednisolone	10%	
Other medication		
Antihypertensive	20%	
Antihyperlipidemia	30%	
Smoking status		
Current smoker	10%	
Past smoker	30%	
Never smoked	60%	

Values are mean ± SD/%, N = 10. RF; rheumatoid factor, CCP; cyclic citrullinated peptide, CRP; C-reactive protein, DAS; disease activity score, MTX; methotrexate, SSZ; sulphasalazine.

6.3.1 Compliance

Compliance to training was excellent, of the 24 scheduled sessions, participants completed on average 22.3 sessions (range 17–24 sessions), i.e. 92.9% of the sessions.

6.3.2 Cardio-respiratory Fitness and Function

Cardio-respiratory fitness improved significantly after the 8 week exercise programme (p = 0.021) (see Figure 6.1 and Table 6.5). Relative to baseline, fitness improved by 13% (step test), lower body strength improved by 54% (sit to stand test), and agility improved by 17% (8ft up and go test). See Table 6.5.

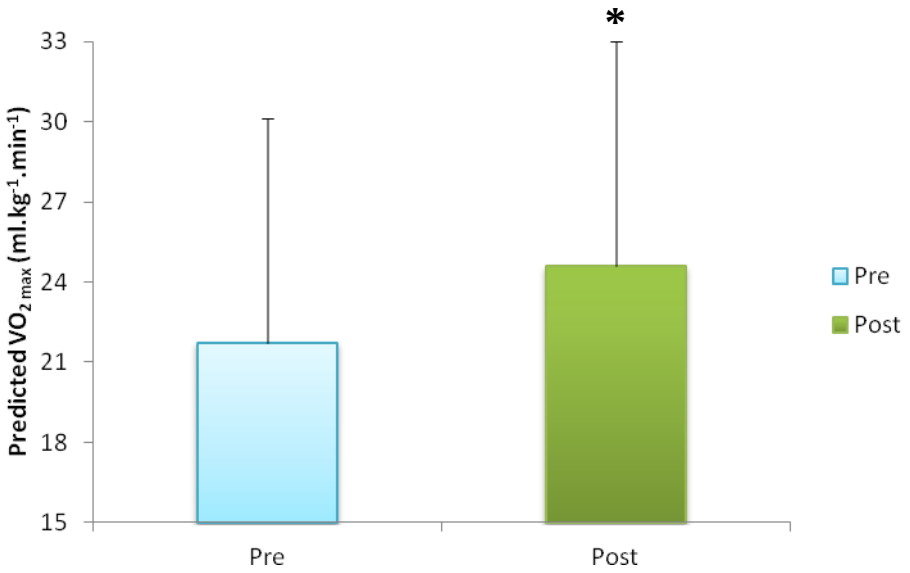

Figure 6.1 Predicted $VO_{2\,max}$ as assessed by the step test before and after 8 weeks of supervised group exercise in patients with RA. *Significant difference between pre and post test scores, $p < 0.05$. Values are mean ± SD, N = 10.

Table 6.5 Effect of 8 weeks of supervised group exercise on fitness, lower body strength and agility.

Fitness and Function	PRE	POST	*P*	Effect Size
Predicted $VO_{2\,max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	21.7 ± 8.4	24.6 ± 8.4	0.021*	0.48
30 second sit to stand (n)	11.1 ± 2.6	17.1 ± 1.7	0.000*	0.90
8 ft Up & Go (seconds)	5.9 ± 0.4	4.9 ± 0.3	0.000*	0.91

Values are mean ± SD, N = 10. *Significant difference between pre and post scores, $P < 0.05$. Effect size was calculated using eta squared, where 0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect.

6.3.3 CVD Risk Factors and Global CVD Risk Scores

Systolic blood pressure decreased by an average of 7 mmHg after 8 weeks of group exercise (p = 0.021). However, there were no major changes to the fasting lipids and glucose. LDL-c did increase by 0.2 mmol·l^{-1} but remained within the normal range (see Table 6.6).

Table 6.6 Effect of 8 weeks of supervised group exercise on blood pressure, fasting lipids and fasting glucose in patients with RA.

CVD Risk Factors	PRE	POST	*P*	Effect Size
SBP (mmHg)	133.2 ± 14.7	125.8 ± 11.9	0.021*	0.46
DBP (mmHg)	76.2 ± 5.9	74.6 ± 7.5	0.448	0.06
TC (mmol·l^{-1})	5.3 ± 0.9	5.4 ± 0.8	0.534	0.04
TG (mmol·l^{-1})	1.3 ± 0.8	1.2 ± 0.7	0.785	0.01
LDL-c (mmol·l^{-1})	2.9 ± 0.7	3.1 ± 0.6	0.034*	0.41
HDL-c (mmol·l^{-1})	1.8 ± 0.4	1.7 ± 0.4	0.112	0.26
Glucose (mmol·l^{-1})	4.9 ± 0.5	4.9 ± 0.6	0.434	0.07
Global CVD Risk Score				
Framingham risk score (percent)	12.75 ± 7.74	11.91 ± 7.70	0.222	0.16
QRISK2 (percent)	17.01 ± 8.30	16.87 ± 8.41	0.670	0.02

Values are mean ± SD, N = 10. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein. *Significant difference between pre and post scores, $P < 0.05$. Effect size was calculated using eta squared, where 0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect.

6.3.4 Body Composition

There was a 9% decrease in body fat percent, 2% decrease in waist circumference and 3% decrease in hip circumference in this RA group following 8 weeks of exercise training. There was an overall reduction in total weight (1.4 kg) and BMI (0.6 kg·m^{-2}). However, these changes were not significant (see Table 6.7).

Table 6.7 Effect of 8 weeks of supervised group exercise on body composition.

Body Composition	PRE	POST	*P*	Effect Size
Weight (kg)	66.8 ± 15.6	65.4 ± 14.2	0.069	0.32
BMI (kg·m^{-2})	25.7 ± 4.4	25.1 ± 3.8	0.056	0.35
Body fat (%)	34.0 ± 12.6	31.0 ± 11.9	0.018*	0.48
Waist (cm)	82.6 ± 11.1	80.8 ± 10.3	0.035*	0.41
Hip (cm)	98.7 ± 9.4	95.4 ± 6.9	0.016*	0.49
Waist:Hip	0.84 ± .06	0.84 ± .07	0.226	0.16

Values are mean ± SD, N = 10.*Significant difference between pre and post scores, $P < 0.05$. Effect size was calculated using eta squared, where 0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect.

6.3.5 RA Disease

The effects of 8 weeks of supervised exercise on inflammation, disease activity, pain, fatigue and QoL are presented in Table 6.8. There was no change in levels of inflammation, however, disease activity (DAS 28 ESR and CRP) and number of tender joints improved significantly. After 8 weeks of training there was a significant improvement in reported arthritis (VAS arthritis), pain, disability (HAQ), fatigue and QoL.

Table 6.8 Effect of 8 weeks of supervised group exercise on specific RA factors.

RA Characteristic	PRE	POST	*P*	Effect Size
ESR ($mm \cdot hr^{-1}$)	3.2 ± 1.9	2.3 ± 0.7	0.081	0.30
CRP ($mg \cdot l^{-1}$)	4.0 ± 0.0	4.8 ± 2.5	0.343	0.10
DAS 28 ESR	2.1 ± 0.7	1.2 ± 0.6	0.002*	0.66
DAS 28 CRP	2.9 ± 0.6	2.2 ± 0.5	0.016*	0.49
Tender joints (n)	2.9 ± 1.9	1.0 ± 1.2	0.016*	0.49
Swollen joints (n)	0.4 ± 0.8	0.0 ± 0.0	0.168	0.20
VAS arthritis (0-100)	27.5 ± 16.0	16.5 ± 10.0	0.040*	0.39
Pain (0-100)	24.1 ± 17.9	12.4 ± 9.5	0.032*	0.42
Fatigue (1-50)	18.8 ± 12.6	11.9 ± 9.2	0.019*	0.48
HAQ (0-3)	.81 ± .65	0.33 ± .29	0.007*	0.57
SF36-Physical health	39.3 ± 9.3	48.6 ± 6.9	0.035*	0.41
SF36-Mental health	51.5 ± 9.2	56.8 ± 4.6	0.014*	0.51
SF36 total score	90.7 ± 11.9	105.5 ± 8.0	0.004*	0.62

Values are mean ± SD, N = 10. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire. *Significant difference between pre and post scores, $P < 0.05$. Effect size was calculated using eta squared, where 0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect.

The QoL measures are shown in greater detail in Figure 6.2. All QoL measures from the SF-36 improved after the 8 week exercise programme, the greatest improvement observed was in physical role limitations.

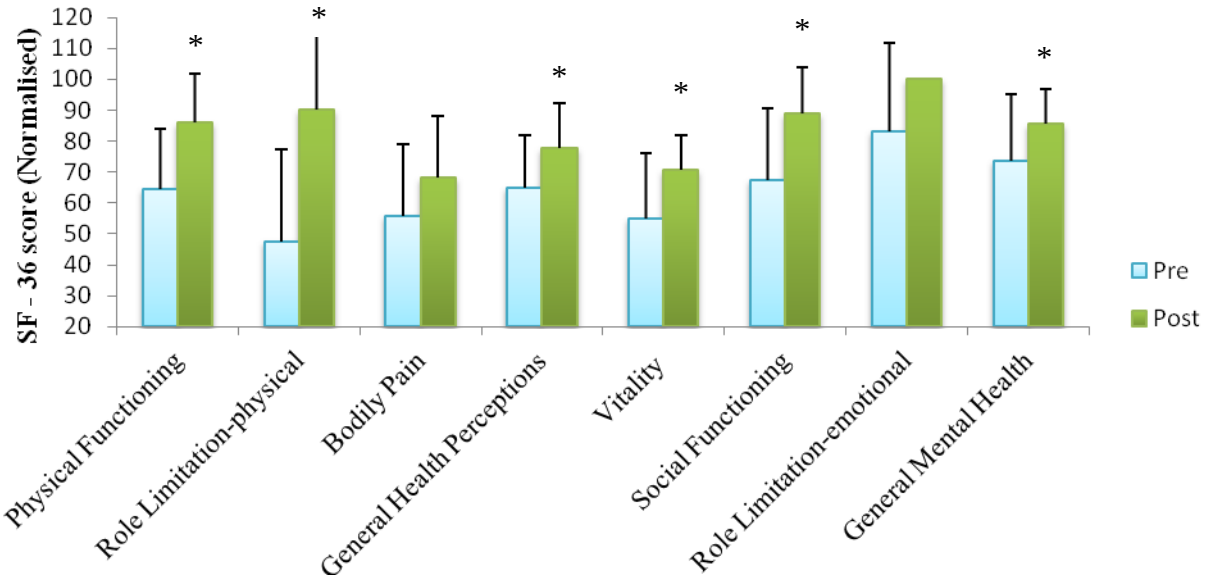

Figure 6.2 Changes in SF-36 scores before and after the 8 week group exercise intervention in patients with RA. Values are mean ± SD, N = 10. *Significant difference between pre and post scores, *P* < 0.05.

6.4 Discussion

To the best of our knowledge this is the first exercise intervention designed to improve the overall cardiovascular health of patients with RA. The current study has shown that 8 weeks of supervised group exercise increased cardio-respiratory fitness and provided improvements not only in cardiovascular health (systolic blood pressure) and body composition (body fat, waist and hip circumference) but also in RA disease symptoms (disease activity, fatigue, pain, disability).

Cardio-respiratory fitness improved significantly by 13%. This improvement in cardio-respiratory fitness demonstrated that the training programme performed in the current study was of sufficient intensity, duration and frequency to elicit such changes. In general it is recommended that aerobic training is performed 3 to 5 times per week, with an intensity of 55% - 90% of HR max and with a duration of 20 to 60 minutes (ACSM, 1998). The current investigation has demonstrated a beneficial effect training 3 times a week, with an intensity of 55% - 85% HR max for 60 minutes. The increase in fitness observed in this study after 8 weeks of exercise training is consistent with findings from previous studies also carried out in patients with RA (Breedland et al., 2011, Neuberger et al., 2007). The results of the present study confirm that a dynamic exercise programme like the one described in this chapter is effective in increasing cardio-respiratory fitness (Häkkinen et al., 2003, Stenstrom and Minor, 2003, Van den Ende et al., 1998). In a systematic review carried out by Van den Ende et al. (1998), improvements in cardio-respiratory fitness ranged from 4 - 33%, these varying results were due to differences in the duration of training which ranged from 8 weeks to 2 years (Van den Ende et al., 1998). As well as improvements in cardio-respiratory fitness, lower body strength improved by 54% (sit to stand test), this finding is greater than that reported by Lemmey et al. (2009) who found only a 30% improvement in sit to stand after 24 weeks of progressive resistance training in a sample of RA patients (Lemmey et al., 2009). The improvements in the sit to stand test observed in the present investigation are similar to the improvements observed by Matsuda et al. (2010), who reported a 59% increase in a group of healthy older adults after a 6 week home based exercise programme. These older adults were on average 7 years older and had a greater BMI than the RA patients investigated in the current study. However, the improvements observed in the present study compare well to

those reported by Matsuda et al. They reported a 25% improvement in agility (Matsuda et al., 2010), whilst in the current investigation agility improved by 17% (8 ft up and go test).

The 8 week exercise programme designed to improve cardio-respiratory fitness also significantly reduced systolic blood pressure by 7 mmHg. The average systolic blood pressure at baseline was 133 mmHg which is clinically classified as within the normal range. However, 8 weeks of aerobic exercise reduced the number of hypertensive patients from five at baseline to three after the exercise intervention. No major changes to fasting lipids and glucose were observed. LDL cholesterol did increase by 0.2 $mmol \cdot l^{-1}$ (6.8%) after the exercise programme and although this was statistically significant, LDL cholesterol remained within the optimum range. This small change in LDL cholesterol could be explained by a normal physiological variation, with data suggesting that the coefficient of biological variation averages at 8.2% (NCEP, 1995). Despite the lack of change in fasting lipids there was a reduction in the Framingham 10 year risk score of 0.8%. Although not significant this is an encouraging finding considering the short duration of the exercise intervention and the fact that age and gender primarily contribute to this risk score.

The literature on the benefits of exercise on cardiovascular risk factors are nonexistent in the RA population (Cairns and McVeigh, 2009) and so can only compare the current findings to those studies carried out on the general population and those on other chronic inflammatory diseases that are similar to RA. The lack of statistically significant improvements in lipids in our sample of RA patients could be due to several reasons. One could be due to the optimal mean baseline values of these variables, especially LDL-c, HDL-c and TG. For example, using the National Institute for Health and Clinical Excellence (NICE) and Department of Health cholesterol guidelines the average baseline values for LDL-c, HDL-c and TG would be classified in the normal range. However, the Joint British Societies (a group of the main UK expert societies involved in cardiovascular disease) recommend different cholesterol limits for people who have, or are at risk of, coronary heart disease. It could be argued that patients with RA would come under this bracket; in which case the recommended lipid levels are less than 4.0 $mmol \cdot l^{-1}$ for total cholesterol and less than 2.0 $mmol \cdot l^{-1}$ for LDL cholesterol. These guidelines match the more stringent recommendations used in the rest of Europe which would mean that the lipid levels observed in this investigation (TC - 5.3 $mmol \cdot l^{-1}$, LDL-c - 2.9 $mmol \cdot l^{-1}$) are higher than the optimal. Another explanation for the lack of effect could be

the short duration of our exercise programme. Eight weeks is potentially not long enough to see a change in lipid levels from exercise alone (Kodama et al., 2007).

Perhaps the lack of alteration of lipid levels is not concerning considering the notion that lipids have a paradoxical association with CVD risk in RA. A recent study suggested that lower TC and LDL-c levels were in fact associated with increased cardiovascular risk (Myasoedova et al., 2011). However, the relationships between lipid levels, inflammation and CVD are believed to be much more complex than that suggested by Myasoedova et al. (2011) and thus the general consensus is that traditional CVD risk management should remain high priority in these high risk patients (Strandberg, 2011).

Previous randomised trials dealing with the effects of exercise on lipids and lipoproteins in adults have led to conflicting results. A meta analysis by Kelley et al. (2004) on the effects of walking on lipids reported significant decreases in LDL-c and TC/HDL-c. On average these exercise programmes lasted 23 weeks where participants walked for 40 minutes 4-5 times a week at an intensity of 65% $VO_{2\ max}$. In this meta-analysis whilst there was a significant improvement in cardio-respiratory fitness no change in body composition was observed (Kelley et al., 2004). Many other studies however have failed to show any differences in lipid profiles, one home-based walking programme which did not include any direct supervision reported that healthy middle-aged women who walked for 30 minutes, four times a week improved their fitness, but showed no change in their cardiovascular risk factors (Davison and Grant, 1995). The authors believed the lack of effect was due to low adherence to the walking programme. Another similar study carried out on sedentary middle aged men also showed no effect on TC or HDL-c after a one-year brisk walking intervention (Stensel et al., 1993). The lack of effect in that study was attributed to the exercise being of insufficient intensity. Both of the reasons outlined in these studies do not apply to the current exercise intervention as it is believed the exercise was of sufficient intensity and the adherence to the programme was excellent.

As well as improvements in cardio-respiratory fitness and systolic blood pressure, 8 weeks of supervised aerobic exercise significantly improved RA patients' body composition. On average body fat percent was reduced by 9%. This remarkable loss in fat mass was accompanied by a 2 cm reduction in waist circumference and 3 cm reduction in hip

circumference. Central adiposity (increased waist circumference) has previously been shown to significantly increase cardiovascular disease risk (Fanghanel et al., 2011). The reason for this is that excess visceral fat is metabolically active, which can cause increases in blood pressure, lipids and insulin resistance (Despres, 2001). Thus, reducing waist circumference can improve an individual's CVD risk. There was an insignificant reduction in total body weight (1.4 kg) and thus little change in RA patients' BMI, which can be partially explained by a 1 kg increase in lean mass (p = 0.215). However, upon further examination of BMI scores before and after the exercise programme the number of patients who had a normal BMI (< 25) increased from 5 to 6, the number of overweight (25-29.9) patients stayed the same (n=3), whilst the number of obese patients was reduced from 2 to 1 (≥ 30). These improvements in body composition are very promising considering patients were exercising for only 8 weeks with no change in their diet. The changes in body composition observed in this investigation are very similar to those reported by Lim et al. (2010). After 8 weeks of aquatic exercise, training 3 times a week, they observed a non significant reduction in BMI and a significant reduction in percent body fat, in a group of patients with knee osteoarthritis (Lim et al., 2010). The results of the current investigation are also supported by Dekker et al. (2007). They examined the beneficial effects of a 12 week aerobic exercise training programme in lean males, obese males and males with type 2 diabetes mellitus. There was no significant reduction in total mass or BMI, however, waist circumference decreased significantly with an average loss of 3 cm around the waist in all three groups (Dekker et al., 2007).

In support of previous literature the beneficial effects of exercise in the present study were achieved without any exacerbation of RA disease. In fact eight weeks of supervised aerobic exercise improved disease activity (DAS 28) by 42.8% (a reduction of 0.9). According to the EULAR response criteria this reduction represents a moderate change when the baseline DAS 28 score is less than 3.2 (Fransen and van Riel, 2005). This reduction in disease activity was surprising considering the very low disease activity of this population at baseline. Disability measured by the HAQ score was reduced by 0.48 (59%). Not only was this statistically significant but this improvement in physical function was also clinically meaningful. In rheumatology an improvement in the HAQ disability index of at least 0.3 from baseline is considered a clinically significant change. Improvements in function due to exercise has received some debate and the beneficial effect on subjective measures of function are not

universal. For example, an intensive PRT programme failed to improve modified HAQ scores in a group of RA patients despite significant improvements in muscle mass and strength (Lemmey et al., 2009). It was concluded that patients involved in that programme had relatively low disability and that the modified HAQ was not sensitive enough to change in a low disability group. Our findings contradict this statement as our group of RA patients also had low disability at baseline and still managed to improve their physical function. Perhaps this finding demonstrates that aerobic exercise is more beneficial for improving physical function than progressive resistance training alone, or perhaps it suggests that RA patients should be encouraged to engage in both aerobic and resistance training in order to experience maximum overall benefit.

Fatigue is a common complaint in patients with RA with 40% experiencing clinically significant fatigue (Wolfe et al., 1996). It is often described as one of the most annoying problems due to the distress and disruption it can cause. Fatigue is defined as 'extreme and persistent tiredness, weakness or exhaustion that can be mental, physical or both' (Hewlett et al., 2005). From the RA fatigue research literature there is little known about how best to assess it and more importantly how to treat it (Repping-Wuts et al., 2009). In the current study after 8 weeks of exercise, fatigue improved by 6.9 points (36%). A change of 5 or more points from baseline is considered a clinically significant reduction in fatigue when using the MAF questionnaire (Goligher et al., 2008). The thesis's findings are consistent with recent research that also suggests that fatigue can be reduced by performing regular exercise (Neuberger et al., 1997). One systematic review explored the effectiveness of nonpharmacological interventions for fatigue (Neill et al., 2006) they also concluded that both aerobic and resistance exercise interventions can reduce RA fatigue.

As well as a clinically significant reduction in fatigue, QoL (SF-36) improved significantly after the 8 week exercise programme. Upon further examination of the individual items, 6 of 8 scales improved significantly after the exercise programme (Figure 6.2). Previous literature on the benefits of exercise on health related QoL has reported mixed results. Bilberg et al. (2005) only reported improvements in physical functioning, vitality and bodily pain after 12 weeks of pool exercise twice a week, in a sample of RA patients. They only examined heart rate at two of the training sessions to monitor intensity of exercise and so they concluded that perhaps the exercise intensity was insufficient throughout the intervention (Bilberg et al.,

2005). It must also be noted that their sample of RA patients had a much higher baseline cardio-respiratory fitness than that observed in this thesis. Other studies that have found a significant improvement in quality of life after exercise training include patients with type 2 diabetes mellitus (Kaplan et al., 1987) and patients with knee osteoarthritis (Rejeski et al., 2002).

The strengths and weaknesses of this pilot study warrant consideration. To the best of our knowledge this was the first study to investigate the beneficial effects of aerobic exercise on CVD risk factors in patients with RA. However, despite significant improvements to patients overall cardiovascular health and general well being, this study is not without limitations. Firstly, RA patients' traditional CVD risk factors including body composition were not markedly elevated at baseline and were much lower than that of the RA patients investigated in Chapter 4 of this thesis. RA patients investigated in the exercise training study had a similar disease duration to patients investigated in the cross sectional study; however, they were on average 4 years older, 8 kg lighter, with smaller waists and hips. Their systolic and diastolic blood pressures were slightly lower whilst their fasting lipids were very similar. RA patients who took part in the training study also had much lower levels of inflammation and disease activity than patients who took part in the cross sectional study. The above differences indicate that the sample of RA patients included in the exercise study were not a true representation of the RA population. Thus, the beneficial effects of exercise on the cardiovascular health of RA patients with more active disease and a worse CVD risk factor profile remains to be determined. Secondly, the sample size in the current study was very small and this investigation lacked a control group, randomisation and blinding. Despite these limitations, this study has designed an effective group exercise intervention that can be carried out in a clinical setting which should be used to form the bases of future research in this area.

6.5 Conclusion

To the best of our knowledge this is the first study to investigate the effects of a short term group exercise programme on overall cardiovascular health and general wellbeing in RA patients. The results of this investigation confirm that moderate to high intensity aerobic exercise is a safe and effective means of improving cardio-respiratory fitness, blood pressure,

body composition, function and symptoms of RA disease itself. It is becoming more evident that traditional risk factors cannot always be relied upon when assessing or aiming to improve the CVD risk of an RA patient. Therefore, factors like obesity and cardio-respiratory fitness become just as important. This investigation has shown that supervised group exercise can help patients improve their cardio-respiratory fitness, aspects of cardiovascular health and body composition. However, future research needs to work on how these advantages can be sustained, improved, including patients with a wide range of disease activity and finally, to determine whether or not treatment like this as part of routine care is financially viable.

7 Chapter 7: General Discussion

The aim of the current PhD thesis was to assess cardio-respiratory fitness and the so called traditional CVD risk factors in patients with RA. Specifically, this project firstly aimed to validate a simple tool that could be used by any health professional to assess RA patient cardio-respiratory fitness levels in a clinical setting, secondly to investigate the association between cardio-respiratory fitness using the step test and CVD risk factors, body composition and RA disease characteristics and finally to determine whether a supervised group exercise programme delivered in a clinical setting could improve the overall cardiovascular health and general well being of these patients.

Poor cardio-respiratory fitness is an acknowledged risk factor for CVD, if not a 'traditional' risk factor in the general population. RA patients' have a greater risk of developing CVD when compared to individuals without RA (Bacon and Townend, 2001). However, despite this knowledge, the routine measurement of cardio-respiratory fitness in a clinical setting is generally nonexistent. The first study discussed here set out to validate a very simple tool that can be used by any health professional to assess RA patients' cardio-respiratory fitness in a clinical setting. The Siconolfi step test is a reasonably valid and reliable measure of cardio-respiratory fitness in these patients, but also importantly it is very simple to perform.

The Siconolfi step test demonstrated that RA patient cardio-respiratory fitness levels were very poor. This thesis aimed to determine whether this poor cardio-respiratory fitness was also associated with a worse CVD risk profile, as previous research suggested that poor physical activity (measured subjectively using a questionnaire) was associated with a worse CVD profile (Metsios et al., 2009). However, despite the level of poor cardio-respiratory fitness observed in RA patients their so called 'traditional' CVD risk factors were not obviously elevated. Poor cardio-respiratory fitness was associated with higher triglycerides and a higher diastolic blood pressure but not with higher systolic blood pressure, total cholesterol and LDL cholesterol as one might expect from the findings of Metsios et al. (2009). However, poor cardio-respiratory fitness was strongly associated with a less favourable body composition. Perhaps the above associations with triglycerides and diastolic blood pressure can be partially explained by the presence of the metabolic syndrome (Lakka et al., 2003). Cardio-respiratory fitness did not directly correlate with the metabolic

syndrome, but 41% of patients were classified as having metabolic syndrome. Perhaps with such strong association between cardio-respiratory fitness and body composition, cardio-respiratory fitness only associates with certain aspects of metabolic syndrome (for instance variables that are associated with excess body fat).

One of the unexpected findings of this work was that 35% of patients with stable RA were unable to complete the step test. This particular test was chosen because the step test was reasonably tolerated by RA patients who participated in the validation study. However, on closer inspection these RA patients were slightly younger, weighed less and had a lower HAQ score. Whereas patients who took part in the cross sectional study were attending a routine clinical appointment. The investigation in Chapters 4 and 5 were carried out in a real life clinical setting and the participants studied were probably a more accurate representation of the RA population. Investigation of the differences between patients who were able and unable to complete the step test has provided some very interesting findings. RA patients unable to complete the step rated their arthritis as worse, more painful and disabling, yet there were no differences in disease duration, inflammation or disease activity between the two groups. In fact the only clear difference between these patients was their body composition. The results of this study (discussed in detail in Chapter 5) suggested that obesity has a major impact on RA patients' perception of their disease and their functional ability.

The prevalence of obesity in this population is concerning. Based on WHO BMI cut offs 27% of RA patients were obese. This is similar to the level of obesity reported in previous research carried out in RA (Armstrong et al., 2006) and higher than the level of obesity reported for the general UK population (HSE, 2009). However, the actual prevalence of obesity is likely to be even higher based on the potential inaccuracy of BMI as a measure of obesity in populations who have altered body composition. If the adapted BMI cut offs as suggested by Stavropoulos – Kalinoglou et al. (2007) were used then 40% of the RA patients studied in the cross sectional study would be classified as obese. This figure may be a more accurate indication of the level of obesity in the RA population as 46% of the RA patients studied in this thesis would be classified as obese based on their body fat percent as measured by bioelectrical impedance analysis. The findings of this thesis support suggestions by Stavropoulos – Kalinoglou et al. (2011) that BMI is likely not a very good measure of obesity in RA and the extent of obesity in this population is probably much worse than originally

perceived. The strong associations between obesity and cardio-respiratory fitness and the detrimental impact obesity appears to have on aspects of RA disease, cardio-respiratory fitness and physical function justify the use of exercise in the treatment of obesity in RA patients. The impact of obesity on the overall health of RA patients was highlighted by Stavropoulos – Kalinoglou et al. (2008). They too emphasized the need to treat obesity in RA and that clinical intervention involving exercise is the likely answer (Stavropoulos-Kalinoglou et al., 2008).

In terms of overall cardiovascular health, poor cardio-respiratory fitness and obesity stand out as two major risk factors for CVD in RA that are currently being ignored by health professionals. Examining the group of RA patients as a whole, their traditional CVD risk factors did not seem obviously elevated. This could be explained by the use of CVD risk lowering medication. However, in the cross sectional study 34% and 41% of RA patients were noted to be hypertensive and dyslipidemic, respectively and not adequately treated. Forty-one percent of RA patients also fulfilled the NCEP criteria for metabolic syndrome, another risk factor for CVD that is not routinely assessed.

Despite providing some very interesting associations and differences amongst the unable and able groups, the cross sectional nature of the second experimental study (Chapter 4) means that the findings do not provide any evidence for causality. They do however; provide important information that may be used as the basis of future research. For instance a larger scale prospective study of cardiovascular health with a main focus on cardio-respiratory fitness and obesity is needed. Future research assessing newly diagnosed RA patients would help us understand whether poor cardio-respiratory fitness and obesity get progressively worse from diagnosis or whether these risk factors already exist at the time of diagnosis. Tracking these CVD risk factors as well as the more traditional risk factors would allow a better understanding on the importance of these factors to the overall cardiovascular health and wellbeing of RA patients. Also, in the cross sectional study, the step test was only performed once by each patient, perhaps some of the RA patients who were unable to complete the step test on that instance would be able to complete the step test on another occasion (e.g. they may feel better, more familiar with the test). Thus, the reliability of the step test in a typical RA population, in a clinical setting is unknown and more research using the step test is required to answer the above question. However, despite the limitations of this

cross sectional study, its findings have made an important contribution to our existing knowledge of RA patients' cardiovascular health. In particular, this study has highlighted that even the more traditional, modifiable CVD risk factors are not being fully controlled. This is a very important finding if the cardiovascular health of RA patients is ever going to be improved.

The final study in this thesis aimed to improve these so called modifiable risk factors, in particular cardio-respiratory fitness and obesity. Another important aspect of this pilot study was to design an exercise intervention that could be performed in groups in a clinical setting. Although only performed in a small group of patients, which was a significant limitation to this study, this group exercise intervention significantly improved cardio-respiratory fitness, aspects of cardiovascular health, body composition and even symptoms of RA disease. This exercise intervention was the first of its kind to investigate the beneficial effects of exercise on traditional CVD risk factors in patients with RA and so it could certainly be suggested that this short term exercise programme could help an RA patient to at least begin to improve their overall cardiovascular health and general well being. However, this pilot study lacked randomisation, blinding, a control group and a larger sample size. All of these criteria need to be fulfilled in future research in order to provide more sound conclusions on the beneficial effects exercise has on the cardiovascular health of RA patients. Future research also needs to include RA patients with more active disease than the patients investigated in this exercise intervention. Including patients with more active disease may also provide more information regarding their cardiovascular health that has not been shown in this thesis.

Despite certain limitations, addressed in the preceding chapters, the combined studies discussed here have advanced our knowledge on RA patients' cardiovascular health, by adding to our understanding of the factors that may contribute to the heightened CVD risk in this population, in particular poor cardio-respiratory fitness and obesity. The new findings also provide support for previous findings that have been subject to quite some debate. In particular this thesis supports one side of the ongoing argument about what obesity actually means in the RA population. Some researchers suggest that obesity is having a protective effect on CVD risk factors and that perhaps obesity is not even a risk factor of CVD in patients with RA (Peeters et al., 2003). The research by Peeters et al. (2003) along with the research that suggests obese patients present with less joint damage (Kaufmann et al., 2003)

promote the idea that obesity is not that detrimental to the RA patient. However, in the current thesis it has been shown that obesity significantly impacts on patients' functional ability and on the perception of their arthritis. They report more pain and disability, but above all these obese patients have a very poor cardio-respiratory fitness. Fitness levels as low as 10-13 $ml \cdot kg^{-1} \cdot min^{-1}$ were observed. This means doing very simple tasks like washing, dressing and grooming oneself requires 74% of their $VO_{2\ max}$ (Tudor-Locke et al., 2009). Therefore, it is unsurprising that a higher HAQ score was observed in these patients. This serious deficiency in cardio-respiratory function illustrates the importance of interventions known to increase $VO_{2\ max}$. Exercise training is so important to delay the age at which cardio-respiratory fitness becomes so limiting that an individual can no longer function independently in activities of daily living. These findings along with the findings from the literature discussed throughout this thesis illustrate the complex nature and importance of these risk factors in individuals with RA.

This thesis has repeatedly demonstrated poor cardio-respiratory fitness and obesity in RA patients, yet these independent CVD risk factors continue to be overlooked. A recent report by Liao (2012) recognised that RA patients have an increased risk of CVD and in this review proposed three questions. How do we estimate risk of CVD in RA? Which interventions decrease CVD risk? And what should be the targets of the interventions? In Liao's report the Framingham risk score is described as the main method for estimating CVD risk. However, it is also acknowledged that this method does not accurately estimate the risk of heart disease in RA and that it likely underestimates risk by approximately 50%. The following is an exact quote from the review

> *"We have much guidance about how to prevent heart disease in RA based on the wealth of studies in the general population. The first, and perhaps the hardest, intervention is a change in habit: eating a well-balanced diet, exercising on a regular basis, and maintaining a healthy weight. We all know how well that works."* (Liao, 2012).

The above quote highlights the problem health professionals are faced with. Maintaining a healthy weight and regular exercise is recognised as a good intervention to help improve cardiovascular health, but because this requires too much effort, exercise is no longer

mentioned and the review continues with a discussion of the use of statins and screening lipids as a means of reducing CVD risk (Liao, 2012). The current thesis has demonstrated the importance of highlighting the need for lifestyle modification. Perhaps if cardio-respiratory fitness and body composition was measured routinely, the reality of the problem might encourage primary care physicians, rheumatologists and their team of health professionals to actually try and do something about it. However, the question arises, who should be responsible for addressing these issues with patients? Is this a matter for primary or secondary care physicians? Within secondary care, limited time means inflammatory disease management takes priority. This would suggest that perhaps this should be dealt with within a primary care setting. However, RA patients with early disease may only see their rheumatologist for months or even years. This "confusion" between both healthcare systems could explain why there are also such a large percentage of patients with untreated hypertension, dyslipidemia and obesity.

An important novel feature of the studies reported here is the use of a submaximal step test to estimate cardio-respiratory fitness in patients with RA instead of the use of physical activity questionnaires to gage how fit and active RA patients actually are. An article by Lee et al. (2010) explained the importance of measuring cardio-respiratory fitness very clearly. Cardio-respiratory fitness and physical activity are often used interchangeably (Lee et al., 2010). However, the measurement of both can often provide very different results (Cuperus et al., 2012). In the cross sectional study (Chapter 4) 35% of RA patients reported having a moderate level of physical activity, however, no association between level of physical activity and cardio-respiratory fitness was observed. The measurement of physical activity using questionnaires relies on self reporting and has been shown to underestimate the association between physical activity and health outcomes (Walsh et al., 2004), whereas the measurement of cardio-respiratory fitness has been shown to have a much stronger association with all-cause mortality. Cardio-respiratory fitness is now believed to be an even stronger predictor of all-cause mortality in comparison to established risk factors like hypertension, smoking, and diabetes mellitus (Myers et al., 2002) and that an improvement in cardio-respiratory fitness, as small as 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ could reduce CVD mortality by as much as 16% (Blair et al., 1995). Because of this, the current thesis along with some previous studies (Kodama et al., 2009, Lee et al., 2010) recommend that cardio-respiratory fitness

should be assessed in a clinical setting and the information provided should be used to make clinical recommendations as part of routine care.

Nonetheless, to make the assessment of cardio-respiratory fitness worthwhile, RA patients need to engage in regular physical activity, if they want to make changes to their overall cardiovascular health and well being. The issue here is that physical inactivity is not just a problem within rheumatology. Health surveys suggest that in the UK 71% of adult women and 61% of adult men do not meet the government's recommendation for physical activity (HSE, 2008). This physical inactivity is thought to cost the NHS £8.2 billion per year which is in addition to the cost of obesity estimated at £4.2 billion per year. Despite this enormous burden on our health system, physical inactivity as a risk factor for many chronic diseases is generally ignored. More traditional risk factors like hypertension, dyslipidemia and diabetes mellitus are recognised as modifiable risk factors for many chronic diseases. They are routinely reviewed during visits to a GP because incentivised interventions are embedded within the primary healthcare system. GP's are financially rewarded for meeting healthcare targets through the Quality and Outcomes Framework. In a recent editorial, it was proposed that physical activity should also be incorporated into a Quality and Outcomes Framework (Weiler and Stamatakis, 2010). This would quickly incorporate physical activity into GP's medical systems, motivate regular follow-ups and promote physical activity within primary care consultations. However, there is one issue with this. GP's are not experts in exercise medicine, exercise prescription and are not trained to give advice on lifestyle modification. Perhaps GP's and specialist doctors who see their patients for specific medical reasons need to refer their patients to suitably trained allied healthcare professionals, like exercise physiologists, to maximise the chances of successful behaviour change. Currently the NHS does not employ exercise specialists; perhaps the focus should be on the employment of exercise physiologists as recognised healthcare professionals. This could be quite cost effective considering physical inactivity and obesity cost the NHS approximately £12.4 billion a year.

7.1 Conclusion

The work presented in the current thesis is the first to incorporate measures of cardio-respiratory fitness, body composition and RA disease whilst investigating the traditional CVD risk factors of an RA population. To date no other investigation has measured all of these factors together in a clinical setting. In the investigated RA population there was little range in their cardio-respiratory fitness level, i.e. all patients had a low cardio-respiratory fitness and thus no outstanding associations between cardio-respiratory fitness and traditional CVD risk factors were observed. This could be partially explained by a large percentage of patients receiving CVD risk lowering medication. However, what is evident from this thesis is that RA patients are suffering from the effects of being unfit and overweight. Poor cardio-respiratory fitness and obesity is having a significant impact on patients' physical ability and the perception of their RA disease. The present investigation has shown that cardio-respiratory fitness and obesity can easily be assessed in a clinical setting and should be incorporated as part of routine care. Based on this information RA patients should be given the necessary advice on how to improve their overall cardiovascular health and general well being. A group exercise intervention like the one outlined in this thesis could help patients adopt a healthier lifestyle. This along with careful management of the more traditional CVD risk factors could help reduce the risk of CVD mortality in this population.

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9 Appendices

Appendix 1: Normative Data on Fitness Levels (Heywood, 1998)

Table 1 Normative data for females (values in ml·kg^{-1}·min^{-1})

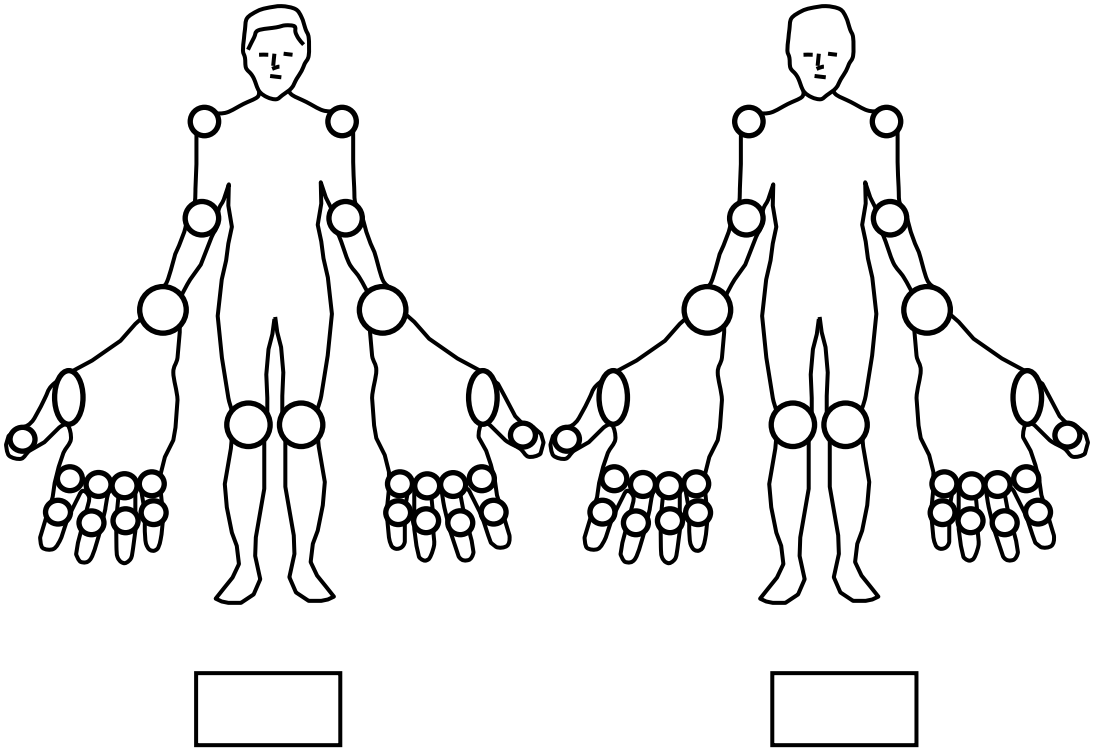
Age	Very Poor	Poor	Fair	Good	Excellent	Superior
13-19	<25.0	25.0 - 30.9	31.0 - 34.9	35.0 - 38.9	39.0 - 41.9	>41.9
20-29	<23.6	23.6 - 28.9	29.0 - 32.9	33.0 - 36.9	37.0 - 41.0	>41.0
30-39	<22.8	22.8 - 26.9	27.0 - 31.4	31.5 - 35.6	35.7 - 40.0	>40.0
40-49	<21.0	21.0 - 24.4	24.5 - 28.9	29.0 - 32.8	32.9 - 36.9	>36.9
50-59	<20.2	20.2 - 22.7	22.8 - 26.9	27.0 - 31.4	31.5 - 35.7	>35.7
60+	<17.5	17.5 - 20.1	20.2 - 24.4	24.5 - 30.2	30.3 - 31.4	>31.4

Table 2 Normative data for males (values in ml·kg^{-1}·min^{-1}).

Age	Very Poor	Poor	Fair	Good	Excellent	Superior
13-19	<35.0	35.0 - 38.3	38.4 - 45.1	45.2 - 50.9	51.0 - 55.9	>55.9
20-29	<33.0	33.0 - 36.4	36.5 - 42.4	42.5 - 46.4	46.5 - 52.4	>52.4
30-39	<31.5	31.5 - 35.4	35.5 - 40.9	41.0 - 44.9	45.0 - 49.4	>49.4
40-49	<30.2	30.2 - 33.5	33.6 - 38.9	39.0 - 43.7	43.8 - 48.0	>48.0
50-59	<26.1	26.1 - 30.9	31.0 - 35.7	35.8 - 40.9	41.0 - 45.3	>45.3
60+	<20.5	20.5 - 26.0	26.1 - 32.2	32.3 - 36.4	36.5 - 44.2	>44.2

Appendix 2: Disease Activity Score 28 (DAS 28)

TENDER JOINTS SWOLLEN JOINTS



VAS SCALE: _____

(In the past week how would you rate your rheumatoid arthritis from the best it has ever been to the worst it has ever been?)

PAIN _____

(How would you rate your current pain?)

Appendix 3: Health Assessment Questionnaire (HAQ)

HAQ - Please check the response which best describes your usual abilities OVER THE PAST

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE To do	SCORE
	0	1	2	3	
Dressing and Grooming Are you able to:					
Dress yourself, including tying shoelaces and buttons?					
Shampoo your hair?					
Rising Are you able to:					
Stand up from an armless straight chair?					
Get in and out of bed?					
Eating Are you able to:					
Cut your meat?					
Lift a cup or glass to your mouth?					
Open a new carton of milk (or soap powder)?					
Walking Are you able to:					
Walk outdoors on flat ground?					
Climb up five steps?					
Hygiene Are you able to:					
Wash and dry your body?					
Take a tub bath?					
Get on and off the toilet?					
Rising Are you able to:					
Reach and get down a 5lb object from just able your head					
Bend down to pick up clothing off the floor?					
Grip Are you able to:					
Open car doors?					
Open jars which have been previously opened?					
Turn taps on and off?					
Activities Are you able to?					
Run errands and shop?					
Get in and out of a car?					
Do chores such as vacuuming, housework, light gardening?					

Please tick any AIDS OR DEVICES that you usually use for any of these activities:

Cane (W) ○ Walking frame (W) ○ Built up or special utensils ○ Crutches ○ Wheelchair ○

Special chair ○ Raised toilet seat ○ Bath seat ○ Bath rail ○ Long handled appliances for reach ○

Jar opener ○ Devices used for dressing (button hooks, zipper pull, shoe horn) ○

Please tick any categories for which you usually need help from another person

Dressing ○ Eating ○ Rising ○ Walking ○ Hygiene ○ Reach ○ Gripping ○ Housework ○

Appendix 4: Equations to predict $VO_{2\ max}$

Step 1: calculate VO_2

Stage 1: VO_2 (litres/minute) = (16.287 x body weight in kg)/1000

Stage 2: VO_2 (litres/minute) = (24.910 x body weight in kg)/1000

Stage 3: VO_2 (litres/minute) = (33.533 x body weight in kg)/1000

Step two: calculate uncorrected $VO_{2\ max}$

Uncorrected $VO_{2\ max}$ (liters/minute) = stage VO_2/%$VO_{2\ max}$

Where:

%$VO_{2\ max}$ = (0.769 x stage HR) – 48.5 for men

%$VO_{2\ max}$ = (0.667 x stage HR) – 42 for women

Step three: calculate $VO_{2\ max}$

$VO_{2\ max}$ male (liters/minute) = (0.348 x uncorrected VO_{2max}) - (0.035 x age in years) + 3.011

$VO_{2\ max}$ female (liters/minute) = (0.302 x uncorrected VO_{2max}) - (0.019 x age in years) + 1.593

Appendix 5: International Physical Activity Questionnaire (IPAQ)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ)

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.

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*

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.

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*

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 might do 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*

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.

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

Appendix 6: Borg RPE Scale (6-20)

rating	description
6	NO EXERTION AT ALL
7	EXTREMELY LIGHT
8	
9	VERY LIGHT
10	
11	LIGHT
12	
13	SOMEWHAT HARD
14	
15	HARD (HEAVY)
16	
17	VERY HARD
18	
19	EXTREMELY HARD
20	MAXIMAL EXERTION

Appendix 7: Does gender have an impact on the association between fitness/step ability and RA disease, body composition and CVD risk factors?

Methods

In order to determine whether gender had an impact on the associations between cardio-respiratory fitness and RA disease, body composition and CVD risk factors or whether female **'unable'** patients were any different to male **'unable'** patients; the group of 100 RA patients were split into two groups – females (n=69) and males (n=31). The data analysis performed in chapter 4 was repeated for females and males separately.

Results

The female results will be presented first followed by the results for the male group.

Fitness in Females

RA Factors

Fitness did not correlate with any of the RA disease variables in female patients ($p > 0.05$).

Body Composition

Fitness correlated significantly with **weigh**t ($r = -0.598$, $p = 0.000$), **BMI** ($r = -0.620$, $p = 0.000$), **body fat percent** ($r = -0.603$, $p = 0.000$), **waist circumference** ($r = -0.588$, $p = 0.000$), **hip circumference** ($r = -0.565$, $p = 0.000$) when adjusting for age.

CVD Risk Factors

Fitness only correlated significantly with glucose in female RA patients ($r_s = -0.376$, $p = 0.034$).

Hierarchical multiple regression was used to assess the ability of two measures (body fat percent, HAQ) to predict level of fitness. HAQ was entered at step 1, explaining 0.1% of the

variance in fitness levels (R square change 0.001). After entry of body fat percent at step 2 the total variance explained by the model as a whole was 19.8% (F (2,43) = 5.32, p = 0.009). Body fat percent explained an additional 19.7% of the variance in fitness, after controlling for HAQ (R square change 0.197, F change (1,43) = 10.56, p = 0.002). In the final model, only body fat percent was significant (beta -0.45, p = 0.002).

Step Test

33% (23/69) of female RA patients were unable to complete the step test. To analyse this population in more detail we compared this group **'Unable group'** to those patients who were **'able'** to complete the step test.

RA Factors

MANOVA was performed to investigate the differences in RA disease variables. There was a significant difference between patients able and unable to complete the step test on the combined variables (F (11, 55) = 4.21, p = 0.000, Wilks' Lamda = 0.54; partial eta squared = 0.46). When the results for the dependent variable were considered separately, the only differences to reach statistical significance, using a Bonferroni adjusted alpha level of 0.004, was **VAS arthritis** (F (1, 65) = 16.37, p = 0.000, partial eta squared = 0.20) and **HAQ** (F (1, 65) = 28.54, p = 0.000, partial eta squared = 0.31). See Table 1.

Table 1 RA characteristics of unable and able female patients.

RA Characteristic	Unable (n = 23)	Able (n = 46)	*P*
Age (years)	61.3 ± 8.3	56.8 ± 11.1	0.104
Disease duration (years)	11.9 ± 11.9	10.1 ± 9.6	0.489
ESR ($mm \cdot hr^{-1}$)	21.0 ± 13.4	13.8 ± 11.9	0.029
CRP ($mg \cdot l^{-1}$)	18.0 ± 24.4	7.1 ± 12.7	0.019
Tender joints (n)	2.1 ± 3.5	2.5 ± 5.1	0.771
Swollen joints (n)	0.4 ± 1.4	0.5 ± 1.4	0.801
VAS arthritis (0-100)	48.4 ± 22.5	25.4 ± 21.2	0.000*
Pain (0-100)	37.5 ± 33.0	18.5 ± 26.1	0.013
DAS 28 ESR	3.2 ± 1.1	2.5 ± 1.5	0.060
DAS 28 CRP	3.1 ± 0.9	2.6 ± 1.2	0.111
HAQ (0-3)	1.6 ± 0.6	0.7 ± 0.7	0.000*

Values are mean ± SD, N = 69. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

Chi squared analysis revealed no significant association between step ability and DMARD group (χ^2 (1, n = 69) = 3.45, p = 0.178, phi = 0.22), steroid exposure (χ^2 (1, n = 69) = 2.30, p = 0.129, phi = -0.18), presence of rheumatoid factor (χ^2 (2, n = 69) = 3.38, p = 0.184, phi = 0.22) or CCP positivity (χ^2 (2, n = 69) = 3.78, p = 0.151, phi = 0.23).

Body Composition

MANOVA was performed to investigate the differences in body composition variables between the step ability groups. There was a significant difference between patients able and unable to complete the step test on the combined variables (F (6, 61) = 3.57, p = 0.004, Wilks' Lamda = 0.74; partial eta squared = 0.26). When the results for the dependent variable were considered separately, all body composition variables except wasit:hip reached statistical significance, using a Bonferroni adjusted alpha level of 0.008. (Table 5.2) **Weight** (F (1, 66) = 8.1, p = 0.006, partial eta squared = 0.11); **BMI** (F (1, 66) = 15.7, p = 0.000, partial eta squared = 0.19); **body fat percent** (F (1, 66) = 11.4, p = 0.001, partial eta squared = 0.15); **waist circumference** (F (1, 66) = 15.7, p = 0.000, partial eta squared = 0.19); **hip circumference** (F (1, 66) = 11.1, p = 0.001, partial eta squared = 0.14). Inspection of the mean scores indicated that patients unable to complete the step test had a less favourable body composition. Means and SD are shown below in Table 2.

Table 2 Body composition of female RA patients.

Body Composition	Unable (n = 23)	Able (n = 46)	*P*
Weight (kg)	78.65 ± 16.90	68.08 ± 12.93	0.006
BMI (kg·m^{-2})	31.56 ± 6.27	26.26 ± 4.54	0.000
Body Fat (%)	50.72 ±14.41	40.24 ± 10.71	0.001
Waist (cm)	94.95 ± 12.01	83.98 ± 10.03	0.000
Hip (cm)	106.64 ± 12.61	97.38 ± 9.67	0.001
Waist:Hip	0.89 ± 0.04	0.86 ± 0.06	0.043

Values are mean ± SD, N = 69. BMI; body mass index

Chi squared analysis revealed a significant association between step ability and BMI category (χ^2 (1, n = 69) = 11.09, p = 0.001, phi = -0.40), and body fat percentage category (χ^2 (2, n = 69) = 5.92, p = 0.050, phi = 0.30). Unable patients had a greater prevalence of obesity.

Traditional CVD risk factors

MANOVA revealed no significant difference in CVD risk factors (SBP, DBP, fasting lipids and glucose) between the two groups (F (10, 36) = 0.83, p = 0.604). See Table 3.

Table 3 CVD risk factors of female RA patients.

CVD Risk Factors	Unable (n = 23)	Able (n = 46)	*P*
SBP (mmHg)	145.00 ± 19.10	137.27 ± 21.29	0.249
DBP (mmHg)	84.21 ± 9.17	81.51 ± 11.94	0.454
TC (mmol·l^{-1})	5.11 ± 1.11	5.42 ± 1.17	0.418
TG (mmol·l^{-1})	1.59 ± 0.77	1.41 ± 0.79	0.475
LDL-c (mmol·l^{-1})	2.92 ± 0.96	3.17 ± 1.11	0.469
HDL-c (mmol·l^{-1})	1.47 ± 0.36	1.61 ± 0.47	0.320
Glucose (mmol·l^{-1})	5.46 ± 1.25	5.04 ± 0.48	0.096
Framingham risk (percent)	14.83 ± 8.63	10.14 ± 6.47	0.046

Values are mean ± SD, N = 69. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

Chi squared analysis revealed no significant association between step ability and presence of hypertension (medication or high blood pressure) (χ^2 (1, n = 69) = 1.96, p = 0.160, phi = -0.17), dyslipidemia (medication or high cholesterol) (χ^2 (1, n = 69) = 0.34, p = 0.561, phi = 0.07), smoking status (χ^2 (2, n = 69) = 3.46, p = 0.177, phi = 0.22), family history of heart disease (χ^2 (1, n = 69) = 2.25, p = 0.133, phi = 0.18) or Framingham risk score category (low, mod, high risk) (χ^2 (2, n = 69) = 5.27, p = 0.072, phi = 0.29).

Summary of Female Results

Poor cardio-respiratory fitness was strongly associated with a less favourable body composition. BMI and percent body fat had the strongest associations with fitness, the same finding observed in the total population. No significant associations with RA disease variables were observed but a poor fitness was associated with a higher glucose level. Female RA patients who were unable to complete the step test rated their arthritis as worse and more disabling, similar to that of the total group; reported pain in females was higher but not significantly different. Unsurprisingly, female patients unable to complete the step test had a

significantly worse body composition. No differences in CVD risk factors were observed between the step ability groups.

Fitness in Males

RA Factors

Fitness did not correlate with any of the RA disease variables in male RA patients ($p > 0.05$).

Body Composition

Fitness correlated significantly with **weight** (r = -0.757, $p = 0.000$), **BMI** (r = -0.712, $p = 0.001$), **waist circumference** (r = -0.823, $p = 0.000$), **hip circumference** (r = -0.713, $p = 0.000$) **and waist:hip** (r = -0.488, $p = 0.040$) when adjusting for age. Fitness did not correlate significantly with body fat percent (r = -0.297, $p = 0.231$).

CVD Risk Factors

Fitness did not correlate with any of the CVD risk factors in male RA patients ($p > 0.05$).

Because fitness did not correlate significantly with body fat percent in males the hierarchical multiple regression was performed using waist circumference. Hierarchical multiple regression was used to assess the ability of two measures (waist circumference, HAQ) to predict level of fitness. HAQ was entered at step 1, explaining 14.4% of the variance in fitness levels (R square change 0.144). After entry of waist circumference at step 2 the total variance explained by the model as a whole was 41.7% (F (2,16) = 5.73, $p = 0.013$). Waist circumference explained an additional 27.3% of the variance in fitness, after controlling for HAQ (R square change 0.273, F change (1,16) = 7.50, $p = 0.015$). In the final model, only **waist circumference** was significant (beta -0.62, $p = 0.015$).

Step Test

Thirty-nine percent (12/31) of male RA patients were unable to complete the step test. To analyse this population in more detail we compared this group **'Unable group'** to those patients who were **'able'** to complete the step test.

RA Factors

MANOVA was performed to investigate the differences in RA disease variables. There was no significant difference between patients able and unable to complete the step test on the combined variables (F (11, 19) = 1.41, p = 0.245, Wilks' Lamda = 0.55; partial eta squared = 0.45). Inspection of the mean scores suggests that patients unable to complete the step reported worse arthritis, more pain and more disability. See Table 4.

Table 4 RA characteristics of unable and able male patients.

RA Characteristic	Unable (n = 12)	Able (n = 19)	*P*
Age (years)	65.3 ± 6.9	61.6 ± 9.7	0.293
Disease duration (years)	9.1 ± 8.1	10.1 ± 4.7	0.674
ESR ($mm \cdot hr^{-1}$)	19.7 ± 14.2	14.9 ± 12.2	0.320
CRP ($mg \cdot l^{-1}$)	19.8 ± 18.1	12.9 ± 18.9	0.328
Tender joints (n)	1.6 ± 2.2	1.3 ± 2.5	0.732
Swollen joints (n)	1.1 ± 2.2	1.4 ± 3.5	0.768
VAS arthritis (0-100)	43.5 ± 28.3	21.7 ± 16.9	0.012
Pain (0-100)	30.6 ± 29.5	12.7 ± 15.1	0.033
DAS 28 ESR	3.1 ± 1.4	2.4 ± 1.4	0.196
DAS 28 CRP	3.1 ± 1.3	2.6 ± 1.1	0.215
HAQ (0-3)	1.2 ± 0.8	0.4 ± 0.5	0.003

Values are mean ± SD, N = 31. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

Chi squared analysis revealed no significant association between step ability and DMARD group (χ^2 (1, n = 31) = 0.38, p = 0.826, phi = 0.11), steroid use (χ^2 (1, n = 31) = 3.45, p = 0.776, phi = -0.16), presence of rheumatoid factor (χ^2 (2, n = 31) = 1.67, p = 0.434, phi = 0.23) or CCP positivity (χ^2 (2, n = 31) = 1.61, p = 0.448, phi = 0.23).

Body Composition

MANOVA was performed to investigate the differences in body composition variables between the step ability groups. There was no significant difference between patients able and unable to complete the step test on the combined variables (F (6, 24) = 1.43, p = 0.245, Wilks' Lamda = 0.74; partial eta squared = 0.26). Inspection of the mean scores indicated that patients unable to complete the step test had a slightly less favourable body composition but this was not significant. Means and SD are shown below in Table 5.

Table 5 Body composition of male RA patients.

Body Composition	Unable (n = 12)	Able (n = 19)	*P*
Weight (kg)	80.03 ± 21.24	79.80 ± 11.94	0.969
BMI ($kg \cdot m^{-2}$)	28.29 ± 7.16	26.39 ± 3.19	0.320
Body Fat (%)	25.75. ± 9.77	23.21 ± 4.95	0.345
Waist (cm)	101.33 ± 14.61	95.84 ± 9.13	0.206
Hip (cm)	100.67 ± 10.64	99.74 ± 7.31	0.775
Waist:Hip	1.00 ± 0.07	0.95 ± 0.05	0.030

Values are mean ± SD, N = 31.BMI; body mass index

Chi squared analysis revealed no significant association between step ability and BMI category (χ^2 (1, n = 31) = 0.40, p = 0.527, phi = -0.11), or body fat percentage category (χ^2 (2, n = 31) = 3.69, p = 0.157, phi = 0.35). Unable patients did not have a greater prevalence of obesity.

Traditional CVD Risk Factors

MANOVA revealed no significant difference in CVD risk factors (SBP, DBP, fasting lipids and glucose) between the two groups, F (10, 12) = 2.03, p = 0.122. See Table 6.

Table 6 CVD risk factors of male RA patients.

CVD Risk Factors	Unable (n = 12)	Able (n = 19)	*P*
SBP (mmHg)	145.44 ± 28.89	140.86 ± 14.07	0.614
DBP (mmHg)	78.67 ± 8.23	80.14 ± 11.82	0.748
TC ($mmol \cdot l^{-1}$)	5.12 ± 1.48	5.35 ± 1.13	0.680
TG ($mmol \cdot l^{-1}$)	2.02 ± 0.91	1.42 ± 0.49	0.053
LDL-c ($mmol \cdot l^{-1}$)	3.09 ± 1.37	3.31 ± 0.91	0.657
HDL-c ($mmol \cdot l^{-1}$)	1.06 ± 0.23	1.43 ± 0.37	0.015
Glucose ($mmol \cdot l^{-1}$)	5.77 ± 1.49	5.46 ± 1.20	0.613
Framingham risk (percent)	31.32 ± 11.13	23.10 ± 8.88	0.063

Values are mean ± SD, N = 31. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

Chi squared analysis revealed no significant association between step ability and presence of hypertension (medication or high blood pressure) (χ^2 (1, n = 31) = 0.85, p = 0.355, phi = -0.17), dyslipidemia (medication or high cholesterol) (χ^2 (1, n = 31) = 0.18, p = 0.675, phi = 0.08), smoking status (χ^2 (2, n = 31) = 1.17, p = 0.558, phi = 0.19), or family history of heart disease (χ^2 (1, n = 31) = 0.52, p = 0.470, phi = -0.13).

Chi squared analysis revealed a significant association between step ability and Framingham risk score category (low, mod, high risk) (χ^2 (2, n = 31) = 6.29, p = 0.043, phi = 0.48).

Summary of Males Results

Poor fitness was strongly associated with a less favourable body composition. However, unlike in females, waist circumference had the strongest association in male RA patients. Body fat percent was not associated with fitness level. No significant associations with RA disease variables or CVD risk factors between the step ability groups were observed. Male RA patients who were unable to complete the step test did not differ significantly in terms of their RA disease variables. Upon further examination of their mean scores they did seem to rate their arthritis as worse, more painful and more disabling, however this did not reach statistical significance. One of the major differences observed in male RA patients was that there was no significant difference in body composition between patients who were unable or able to complete the step test. No differences in CVD risk factors were observed.

Discussion

These results suggest that obesity may have a greater impact on physical ability and perception of RA disease in female RA patients than in male RA patients. BMI and body fat percent seem to be the greatest predictors of fitness and step ability in females whilst waist circumference has the most significant association with level of fitness in males. There is a very distinct pattern emerging from the results of chapter 4 and 5 and that is that obesity has a significant impact on level of fitness, step ability and how patients, especially females, perceive their arthritis, pain and disability. Despite obesity being a worldwide problem, research on obesity in RA is surprisingly very limited. But being obese has been shown to reduce level of physical activity and causing disability in everyday tasks (Mattsson et al., 1997). Larsson and Mattsson (2001) investigated the perceived disability and functional limitations in a group of obese women. They found that obese women perceived much greater disability on normal activities of daily living than normal weight women. Activities that involved bending, kneeling and walking upstairs were perceived as being more difficult for obese women (Larsson and Mattsson, 2001). Previous results by Mattsson *et al.*, (1997) suggested that these obese women had a lower maximum oxygen uptake, in other words they were more unfit. This is supported by the findings of the study.

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Appendix 8: Ankle Brachial Pressure Index (ABPI) of RA patients

Ankle brachial pressure index (ABPI) intra reliability

To determine the intra observer reliability of JC, 7 healthy participants were recruited and their ABPI was measured at two time points (approximately one week apart). The mean age of the 7 volunteers was 22 (ranging from 18-29) years. There were 4 females and 3 males. Table 1 shows the raw data for the 7 volunteers where T1 and T2 represent time points one and two respectively.

Table 1. Ankle brachial pressure index (ABPI) raw data for the 7 volunteers

Subject	ABPI right T1	ABPI left T1	ABPI right T2	ABPI left T2
1	1.00	1.04	0.95	0.97
2	1.12	1.16	1.21	1.13
3	1.05	1.03	1.08	1.04
4	1.30	1.41	1.35	1.38
5	1.04	1.08	1.06	1.04
6	1.10	1.00	1.00	1.10
7	1.11	1.15	1.09	1.09

Table 2 demonstrates the results for the intra-observer reliability. The intraclass correlation coefficient (ICC) for the intra-observer reliability was high (> 0.80) for observer JC. There was no significant difference between ABPI results at T1 and T2 as shown by the *p* value in Table 2.

Table 2. Results for intra-observer reliability

	Mean	SD	ICC	*P*
ABPI right T1	1.10	0.10		
ABPI right T2	1.12	0.13	0.869	0.910
ABPI left T1	1.12	0.14		
ABPI left T2	1.11	1.13	0.914	0.461

Ankle brachial pressure index (ABPI) in rheumatoid arthritis (RA)

Introduction

Cardiovascular disease is increased in patients with RA. ABPI is an efficient tool for objectively documenting the presence of lower extremity peripheral arterial disease (Allison et al., 2008). A fall in blood pressure in an artery at the ankle relative to the central blood pressure suggests a stenosis in the arterial conduits somewhere in between the aorta and the ankle. The aim of this investigation was to determine the prevalence of an abnormal ABPI in RA patients and to establish potential associations between APBI and RA disease, CVD risk factors and body composition.

Methods

ABPI was assessed in the 100 RA patients who took part in the cross sectional study (chapter 4 and 5).

Protocol

The ABPI was determined by measuring the systolic blood pressure from both brachial arteries and from both the posterior tibial arteries after the patient had been resting in the supine position for 10 minutes. Systolic blood pressure was recorded using a handheld 5 mHz Doppler (Dopplex D900, Huntleigh, Bedfordshire, England). ABPI was calculated by dividing each ankle pressure by the highest brachial arterial pressure.

Results

98 RA patients had a normal ABPI (0.90-1.30) with only 2 subjects having an ABPI between 0.70 - 0.89 indicating mild disease.

In relation to RA disease ABPI correlated significantly with CRP and HAQ scores, with a lower ABPI associated with higher levels of CRP and worse reported disability. ABPI did not correlate with the other RA disease related factors (see Table 3).

Table 3. Correlations between ABPI and RA disease variables

	ABPI	ESR	CRP	Tender joints	Swollen joints	VAS arthritis	Pain	DAS28 ESR	DAS28 CRP	HAQ	Disease duration	Age
ABPI	x											
ESR	-0.13	x										
CRP	**-0.23***	**0.56***	x									
Tender joints	-0.06	**0.30***	0.17	x								
Swollen joints	-0.04	**0.44***	**0.40***	**0.41***	x							
VAS arthritis	-0.15	**0.33***	**0.29***	**0.49***	**0.33***	x						
Pain	-0.09	0.16	0.10	0.38	0.19	**0.65***	x					
DAS 28 ESR	-0.14	**0.72***	**0.44***	**0.75***	**0.61***	**0.68***	**0.51***	x				
DAS 28 CRP	-0.14	**0.55***	**0.52***	**0.81***	**0.64***	**0.73***	**0.51***	**0.93***	x			
HAQ	**-0.20***	**0.34***	**0.20***	**0.32***	0.09	**0.66***	**0.57***	**0.51***	**0.50***	x		
Disease duration	0.01	-0.02	-0.11	-0.07	-0.07	0.15	0.00	-0.01	-0.02	0.14	x	
Age	-0.09	0.08	-0.03	0.10	0.01	0.19	0.09	0.09	0.07	0.12	**0.25**	x

*$p < 0.05$. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

ABPI correlated significantly with systolic blood pressure but did not correlate with the other traditional CVD risk factors (see Table 4).

Table 4. Correlations between ABPI and CVD risk factors

	ABPI	SBP	DBP	Framingham	TC	TG	LDL	HDL	Glucose
ABPI	x								
SBP	**0.40***	x							
DBP	-0.25	**0.63***	x						
Framingham	-0.11	**0.52***	0.23	x					
TC	0.06	-0.04	0.14	-0.01	x				
TG	0.02	0.15	0.14	0.13	0.04	x			
LDL-c	0.06	-0.02	0.13	0.07	**0.92***	0.09	x		
HDL-c	0.01	-0.16	-0.07	-0.25	**0.35***	**0.37***	0.07	x	
Glucose	-0.36	0.24	0.21	**0.59***	0.03	0.05	0.09	0.17	x

*$p < 0.05$. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

ABPI did not correlate with any of the body composition variables (see Table 5).

Table 5. Correlations between ABPI and Body Composition.

	ABPI	Weight	BMI	Waist	Hip	Waist: Hip	Body fat percent
ABPI	x						
Weight	0.08	x					
BMI	-0.04	**0.87***	x				
Waist	-0.06	**0.88***	**0.82***	x			
Hip	-0.04	**0.85***	**0.87***	**0.84***	x		
Waist: hip	-0.05	**0.39***	**0.29***	**0.63***	0.13	x	
Body fat percent	0.10	**0.44***	**0.73***	**0.33***	**0.63***	**-0.21***	x

Step Test and ABPI

ABPI did not correlate with fitness (r = 0.104, p = 0.409).

Independent samples t test illustrated a significant difference in ABPI values in patients who were **Able** and **Unable** to complete the step test, see Table 6.

Table 6. ABPI of step ability groups, N = 100

Step Ability	Mean	SD	*P*
Able (n=65)	1.09	0.17	
Unable (n=35)	0.97	0.32	0.048*

Discussion

RA patients generally had a normal ABPI indicating no clinical evidence of peripheral vascular disease. Only 2% of RA patients had an abnormal ABPI (< 0.9) with values indicating mild peripheral vascular disease. Interestingly, lower ABPI values were associated with higher levels of inflammation (CRP) and worse reported disability (HAQ). Also, RA patients unable to complete the step test had a lower ABPI when compared to patients who were able to complete the step test.

A study by Theodoridou et al. (2003) investigated ABPI in patients with systemic lupus erythematosus (SLE). The prevalence of abnormal ABPI in the SLE cohort was 37%, however, in this study an ABPI of < 1.0 was considered abnormal based on suggestions by Sacks et al. (2002). In the current RA study, 17% of RA patients had an abnormal ABPI based on the above suggestion by Sacks et al. (2002); this is slightly lower than that reported by Alkaabi et al. (2003), who reported 25% of RA patients had an ABPI < 1.0. However, both of these values are significantly greater than the 2.5% of healthy aged matched controls with an ABPI < 1.0 who were also investigated by Alkaabi et al. (2003). Thus, suggesting that the prevalence of peripheral vascular disease is much higher in RA patients than that of healthy controls. Alkaabi et al. (2003) also found that patients with an ABPI < 1.0 had a significantly higher HAQ score compared to patients with a normal ABPI. This result is

supported by the present investigation in which we also found lower ABPI scores were significantly associated with higher HAQ scores. Patients unable to complete the step test also had a significantly lower ABPI than those who were able to complete the step test. Perhaps this increased disability and poor physical function observed in Chapter 4 can be partially explained by the presence of peripheral arterial obstructive disease.

Despite serum lipids being strong predictors of CVD risk, no significant association between the lipid profile and ABPI was observed in the current study. This finding is in line with the results presented in Chapter 4 of this thesis and other studies (Alkaabi et al., 2003; Kavanaugh et al., 1994). Reduced disease activity has been shown to normalise lipid parameters. The RA patients studied throughout this thesis generally had well controlled disease and so the effects of anti-rheumatic drugs should be taken into account as certain second-line agents may lead to normalisation of the lipid profile (Munro et al., 1997).

The current study highlights the potential increased risk of peripheral vascular disease in patients with RA. Research regarding peripheral vascular disease in RA is limited; however, the findings of this small investigation have provided us with an alternative explanation as to why some RA patients are unable to complete the step test and why these patients report more disability. Perhaps, patients with a lower ABPI genuinely experience more pain or difficulty doing physical tasks. Perhaps, symptoms of a lower ABPI are only experienced whilst doing physical activities, as this is when the muscles in the lower extremities are working hard and require more blood flow than when at rest. However, further work is needed measuring ABPI and other markers of vascular disease in RA patients in order to establish more concrete conclusions.

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Appendix 9: Obesity Categories based on fat percent and revised BMI cut-offs

Table 1. RA disease characteristics of the body fat percent groups

RA Factors	Normal (n = 32)	Overweight (n = 22)	Obese (n = 46)	*P*
Age (years)	60.4 ± 11.1	60.1 ± 9.2	59.0 ± 10.1	0.824
Disease duration (years)	8.9 ± 6.9	11.2 ± 8.3	11.0 ± 10.9	0.534
ESR ($mm \cdot hr^{-1}$)	19.5 ± 16.9	14.3 ± 11.9	14.9 ± 9.0	0.213
CRP ($mg \cdot l^{-1}$)	14.3 ± 20.8	12.8 ± 18.8	10.2 ± 15.7	0.613
Tender joints (n)	1.5 ± 3.5	1.6 ± 2.5	2.6 ± 5.0	0.463
Swollen joints (n)	1.3 ± 2.9	0.9 ± 2.3	0.3 ± 0.9	0.135
VAS arthritis (0-100)	26.7 ± 22.7	30.7 ± 19.6	35.9 ± 26.2	0.242
Pain (0-100)	17.8 ± 23.6	19.0 ± 21.1	28.4 ± 32.2	0.196
DAS28 ESR	2.7 ± 1.5	2.6 ± 1.4	2.8 ± 1.3	0.840
DAS28 CRP	2.7 ± 1.2	2.8 ± 1.1	2.80 ± 1.2	0.870
HAQ (0-3)	0.7 ± 0.7	0.8 ± 0.8	1.0 ± 0.8	0.258

Values are mean ± SD, N = 100. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

Table 2. CVD risk factors and global CVD risk scores of the body fat percent groups

CVD Risk Factors	Normal (n = 32)	Overweight (n = 22)	Obese (n = 46)	*P*
SBP (mmHg)	139.1 ± 20.3	145.5 ± 19.7	139.5 ± 21.7	0.655
DBP (mmHg)	80.7 ± 10.2	81.1 ± 12.6	82.0 ± 10.9	0.997
TC ($mmol \cdot l^{-1}$)	5.0 ± 1.1	5.4 ± 1.4	5.5 ± 1.1	0.380
TG ($mmol \cdot l^{-1}$)	1.34] ± 0.7	1.4 ± 0.6	1.7 ± 0.8	0.061
LDL-c ($mmol \cdot l^{-1}$)	3.0 ± 1.0	3.3 ± 1.2	3.2 ± 1.0	0.732
HDL-c ($mmol \cdot l^{-1}$)	1.4 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	0.909
Glucose ($mmol \cdot l^{-1}$)	5.2 ± 1.1	5.2 ± 0.4	5.4 ± 1.1	0.168
Current smoker (n)	8	4	11	-----
Global CVD Risk Scores				
Framingham risk (percent)	19.4 ± 13.6	18.2 ± 7.1	13.5 ± 9.7	0.934
QRISK2 (percent)	23.3 ± 16.5	22.7 ± 12.9	15.9 ± 12.1	0.970
Metabolic syndrome (n)	8	10	23	-----

Values are mean ± SD, N = 100. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

Table 3. RA characteristics of the revised BMI groups (Stavropoulos-Kalinoglou et al., 2009)

RA Factors	Normal (n = 20)	Overweight (n = 40)	Obese (n = 40)	*P*
Age (years)	59.2 ± 11.3	60.3 ± 10.1	59.4 ± 9.8	0.901
Disease duration (years)	9.9 ± 7.4	10.2 ± 8.9	10.7 ± 10.5	0.953
ESR ($mm \cdot hr^{-1}$)	15.5 ± 14.7	16.2 ± 14.3	16.8 ± 10.3	0.936
CRP ($mg \cdot l^{-1}$)	13.6 ± 22.4	11.8 ± 19.3	11.8 ± 14.4	0.927
Tender joints (n)	0.7 ± 1.3	2.4 ± 5.3	2.4 ± 3.6	0.239
Swollen joints (n)	0.8 ± 2.9	0.9 ± 2.2	0.6 ± 1.4	0.774
VAS arthritis (0-100)	24.3 ± 15.7	31.9 ± 25.1	35.6 ± 25.8	0.229
Pain (0-100)	13.7 ± 21.9	16.4 ± 21.4	34.1 ± 32.2	0.004
DAS28 ESR	2.3 ± 1.2	2.7 ± 1.6	3.0 ± 1.3	0.165
DAS28 CRP	2.3 ± 0.9	2.8 ± 1.2	2.9 ± 1.2	0.248
HAQ (0-3)	0.7 ± 0.7	0.8 ± 0.7	1.1 ± 0.8	0.095

Values are mean ± SD, N = 100. ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, DAS; disease activity score, VAS; visual analogue scale, HAQ; health assessment questionnaire.

Table 4. CVD risk factors and global CVD risk scores of the revised BMI groups (Stavropoulos-Kalinoglou et al., 2009)

CVD Risk Factors	Normal (n = 20)	Overweight (n = 40)	Obese (n = 40)	*P*
SBP (mmHg)	132.0 ± 21.8	144.7 ± 19.0	140.5 ± 21.2	0.194
DBP (mmHg)	76.0 ± 10.3	83.4 ± 10.2	81.9 ± 11.4	0.124
TC ($mmol \cdot l^{-1}$)	5.1 ± 1.3	5.3 ± 1.2	5.4 ± 1.1	0.761
TG ($mmol \cdot l^{-1}$)	1.2 ± 0.8	1.4 ± 0.5	1.8 ± 0.8	0.015
LDL-c ($mmol \cdot l^{-1}$)	2.9 ± 1.1	3.2 ± 1.1	3.1 ± 1.1	0.670
HDL-c ($mmol \cdot l^{-1}$)	1.6 ± 0.4	1.5 ± 0.5	1.4 ± 0.4	0.229
Glucose ($mmol \cdot l^{-1}$)	5.1 ± 0.9	5.2 ± 09	5.5 ± 1.2	0.311
Current smoker (n)	6	10	7	-----
Global CVD Risk Scores				
Framingham risk (percent)	15.3 ± 12.9	18.2 ± 10.9	15.1 ± 10.1	0.646
QRISK2 (percent)	18.9 ± 14.2	21.7 ± 15.2	18.2 ± 13.3	0.800
Metabolic syndrome (n)	2	15	24	-----

Values are mean ± SD, N = 100. SBP; systolic blood pressure, DBP; diastolic blood pressure, TC; total cholesterol, TG; triglycerides, LDL-c; low density lipoprotein, HDL-c; high density lipoprotein.

Appendix 10: Fitness Test Recommendations

Table 1 Recommended 30 second sit to stand ranges for males (Jones & Rikli, 2002).

Age	below average	average	above average
60-64	< 14	14 to 19	> 19
65-69	< 12	12 to 18	> 18
70-74	< 12	12 to 17	> 17
75-79	< 11	11 to 17	> 17
80-84	< 10	10 to 15	> 15
85-89	< 8	8 to 14	> 14
90-94	< 7	7 to 12	> 12

Table 2 Recommended 30 second sit to stand ranges for females (Jones & Rikli, 2002).

Age	below average	average	above average
60-64	< 12	12 to 17	> 17
65-69	< 11	11 to 16	> 16
70-74	< 10	10 to 15	> 15
75-79	< 10	10 to 15	> 15
80-84	< 9	9 to 14	> 14
85-89	< 8	8 to 13	> 13
90-94	< 4	4 to 11	> 11

Table 3 Recommended 8ft up and go ranges for males (Jones & Rikli, 2002).

Age	below average	average	above average
60-64	> 5.6	5.6 to 3.8	< 3.8
65-69	> 5.7	5.7 to 4.3	< 4.3
70-74	> 6.0	6.0 to 4.2	< 4.2
75-79	> 7.2	7.2 to 4.6	< 4.6
80-84	> 7.6	7.6 to 5.2	< 5.2
85-89	> 8.9	8.9 to 5.3	< 5.3
90-94	> 10.0	10.0 to 6.2	< 6.2

Table 4 Recommended 8ft up and go ranges for females (Jones & Rikli, 2002).

Age	below average	average	above average
60-64	> 6.0	6.0 to 4.4	< 4.4
65-69	> 6.4	6.4 to 4.8	< 4.8
70-74	> 7.1	7.1 to 4.9	< 4.9
75-79	> 7.4	7.4 to 5.2	< 5.2
80-84	> 8.7	8.7 to 5.7	< 5.7
85-89	> 9.6	9.6 to 6.2	< 6.2
90-94	> 11.5	11.5 to 7.3	< 7.3

Appendix 11: Quality of Life Questionnaire (SF-36)

SF-36 QUESTIONNAIRE

(1992 – Medical Outcomes Trust)

Patient Name: _____ **Date:** _____

1. In general, would you say your health is: (circle one)

   Excellent Very good Good Fair Poor

2. Compared to one year ago, how would you rate your health in general now? (circle one)

   Much better now than one year ago.

   Somewhat better now than one year ago.

   About the same as one year ago.

   Somewhat worse than one year ago.

   Much worse than one year ago.

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Mark each answer with an X)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports			
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing **several** flights of stairs			
e. Climbing **one** flight of stairs			
f. Bending, kneeling or stooping			
g. Walking **more than a mile**			
h. Walking **several blocks**			
i. Walking **one block**			
j. Bathing or dressing yourself			

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Mark each answer with an X)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activites		
b. **Accomplished les**s than you would like		
c. Were limited in the **kind** of work or other activities		
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Mark each answer with an X)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities		
b. **Accomplished les**s than you would like		
c. Didn't do work or other activities as **carefully** as usual		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (circle one)

Not at all Slightly Moderately Quite a bit Extremely

7. How much bodily pain have you had during the past 4 weeks? (circle one)

None Very mild Mild Moderate Severe Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks – (Mark each answer with an X)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?						
b. Have you been a very nervous person?						
c. Have you felt so down in the dumps that nothing could cheer you up?						
d. Have you felt calm and peaceful?						
e. Did you have a lot of energy?						
f. Have you felt downhearted and blue?						
g. Did you feel worn out?						
h. Have you been a happy person?						
i. Did you feel tired?						

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (circle one)

All of the time Most of the time Some of the time A little of the time None of the time

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people					
b. I am as healthy as anybody I know					
c. I expect my health to get worse					
d. My health is excellent					

Appendix 12: Multidimensional Assessment of Fatigue (MAF)

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE

Instructions: These questions are about fatigue and the effect of fatigue on your activities.

For each of the following questions, circle the number that most closely indicates how you have been feeling during the past week.

For example, suppose you really like to sleep late in the mornings. You would probably circle the number closer to the "a great deal" end of the line. This is where I put it:

Example: To what degree do you usually like to sleep late in the mornings?

1	2	3	4	5	6	7	(8)	9	10

Not at all A great deal

Now please complete the following items based on the past week.

---

1. To what degree have you experienced fatigue?

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

If no fatigue, stop here.

2. How severe is the fatigue which you have been experiencing?

1	2	3	4	5	6	7	8	9	10

Mild Severe

3. To what degree has fatigue caused you distress?

1	2	3	4	5	6	7	8	9	10

No distress A great deal of distress

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

Circle the number that most closely indicates to what degree fatigue has interfered with your ability to do the following activities in the past week. For activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired), check the box.

In the past week, to what degree has fatigue interfered with your ability to:

(NOTE: Check box to the left of each number if you don't do activity)

4. Do household chores

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Not at all A great deal

5. Cook

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Not at all A great deal

6. Bathe or wash

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Not at all A great deal

7. Dress

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Not at all A great deal

8. Work

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Not at all A great deal

9. Visit or socialize with friends or family

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
Not at all A great deal

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

(NOTE: Check box to the left of each number if you don't do activity)

10. Engage in sexual activity

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Not at all A great deal

11. Engage in leisure and recreational activities

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Not at all A great deal

12. Shop and do errands

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Not at all A great deal

13. Walk

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Not at all A great deal

14. Exercise, other than walking

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Not at all A great deal

15. Over the past week, how often have you been fatigued?

☐4 Every day
☐3 Most, but not all days
☐2 Occasionally, but not most days
☐1 Hardly any days

16. To what degree has your fatigue changed during the past week?

☐4 Increased
☐3 Fatigue has gone up and down
☐2 Stayed the same
☐1 Decreased