THE ROLE OF PHYSICAL ACTIVITY ON CARDIOVASCULAR DISEASE RISK IN PATIENTS WITH PSORIASIS

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ABBREVIATIONS

AHA	American Heart Association
AMP's	antimicrobial peptides
APC's	antigen presenting cells
BMI	body mass index
BSA	body surface area
CDMS	Clinical Data Management System
DC's	dendritic cells
DLQI	Dermatology Life Quality Index
DRA	Diastolic Reflection Area
EDTA	Ethylenediamine Tectra-Acetic Acid
eNOS	Endothelial Nitrous Oxide Synthase
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HAQ	Health Assessment Questionnaire
HBA1C	glycated haemoglobin
HDL	high-density lipoprotein
HIIT	high intensity interval training
hs-CRP	high-sensitivity C-reactive protein
HSP	heat shock proteins
ICAM	intercellular adhesion molecule
IFN	interferon
IL	interleukin
IPAQ	International Physical Activity Questionnaire
IQR	inter-quartile range
LDL	low density lipoprotein
LFA	leukocyte function associated antigen
MET	metabolic equivalent

MHC	major histocompatibility complex
MICT	moderate intensity continuous training
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NHS	national health service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NK	natural killer
PAF	platelet activating factor
PASI	Psoriasis Area Severity Index
PUVA	psoralen ultraviolet
PWV	pulse wave velocity
ROS	reactive oxygen species
SAPASI	self-administered psoriasis area severity index
saSPI	self-assessed Simplified Psoriasis Index
sE-selectin	soluble E-selectin
SPI	Simplified Psoriasis Index
Th	T helper
TNF	tumour necrosis factor
UV	ultraviolet
WHO	World Health Organisation

ABSTRACT

Background: Patients with psoriasis have an increased risk of cardiovascular disease (CVD) and traditional CVD risk factors, including the metabolic syndrome, are highly prevalent in the psoriasis population. We postulated that individuals with psoriasis may avoid physical activity, which may contribute to their elevated CVD risk.

Aims: The aims of this PhD were to: i) identify the barriers to cardiorespiratory fitness; ii) determine whether physical activity influences arterial stiffness and cardiorespiratory fitness and iii) identify biomarkers of physical activity and arterial stiffness in patients with psoriasis.

Methods: 404 patients with psoriasis were recruited from primary and secondary care sources in the North West of England. Patients were asked to complete the International Physical Activity Questionnaire and the Dermatology Life Quality Index (DLQI). Analysis of venous blood was performed, and biomarkers, including soluble E-selectin metabolic markers, adipokines, circulatory lipids and inflammatory markers were measured. Participants also had an arterial function assessment using the TensioMed Arteriograph (The Arteriograph Company, Budapest, Hungary).

Results: Over 50% of patients with psoriasis failed to meet the recommended guidelines for exercise, as provided by the American Heart Association. Psoriasis severity impacted on exercise behaviour and the DLQI identified six key psoriasis-specific barriers to physical activity, including: skin sensitivity, embarrassment, clothing choices, social/leisure activities, engagement in sport and treatment of psoriasis. Lipid and glycaemic control was found to have a significant impact on arterial stiffness (PWV), which is a preclinical indicator of future CVD risk. Importantly, we found that regulation of these biochemical parameters could be modulated by physical activity, thus providing a means to diminish the CVD risk of patients with psoriasis. Through arterial function assessment we identified that measurement of

the diastolic reflection area (DRA) had utility as a bed-side measure of exercise profile which could provide a means to measure adherence to exercise in the psoriasis population.

Conclusions: This is the first time exercise engagement, in a psoriasis population, has been investigated in relation to arterial stiffness, cardiorespiratory fitness and biochemical profile. Given the CVD risk in patients with psoriasis, these findings strengthen the need for intervention. PWV and DRA could provide means to monitor future CVD risk and exercise engagement, respectively, in a way that is objective, non-invasive and efficient.

DECLARATION

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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CHAPTER ONE: INTRODUCTION

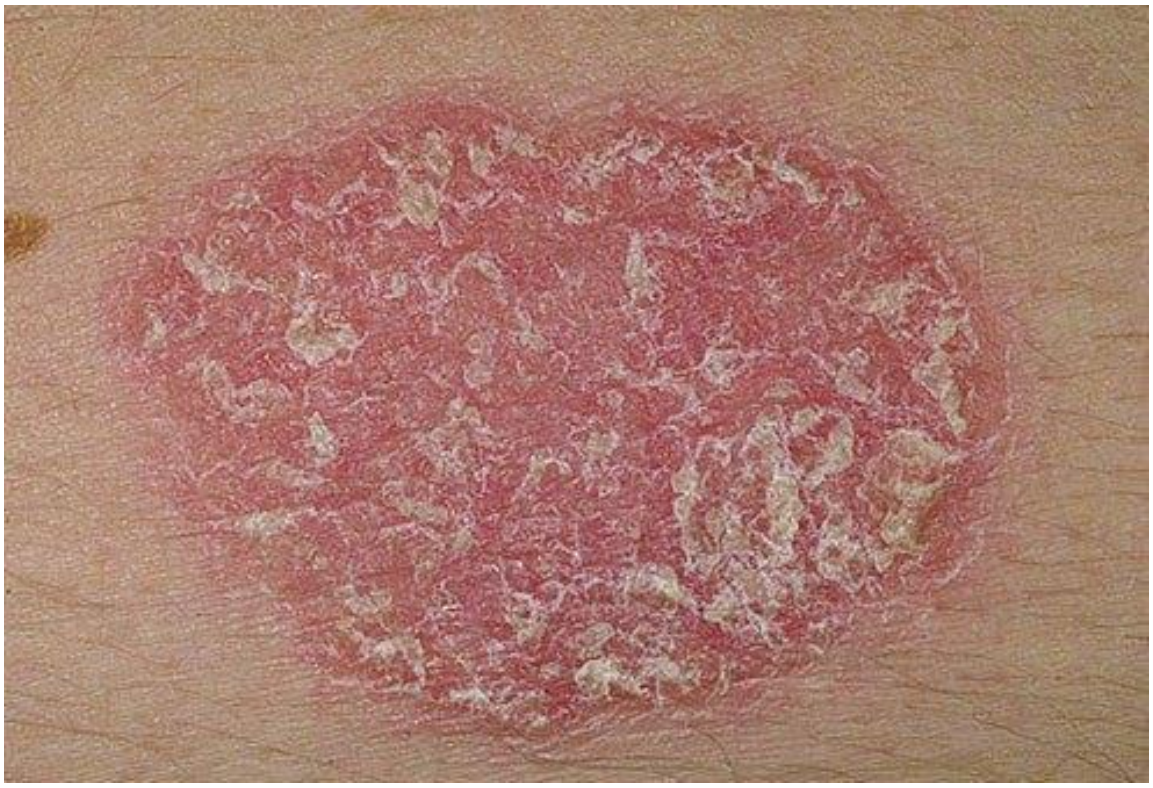
1.1 What is psoriasis?

Psoriasis is a widespread, immune-mediated inflammatory disease of the skin, affecting approximately 2-3% of the UK population (Fry, 1988, Parisi et al., 2013). A bimodal age of onset of psoriasis has been recognised in various large studies (Langley et al., 2005). Henseler and Christophers examined 2147 psoriasis patients and found that there are two clinical phenotypes of psoriasis, Type 1 and Type 2 (Henseler and Christophers, 1985). Patients are classified as having Type 1 psoriasis if they develop the disease prior to or at the age of 40 whilst patients with Type 2 psoriasis develop the disease after the age of 40 (Griffiths et al., 2007). Early onset psoriasis (Type 1) accounts for more than three quarters of all cases and patients with this type of psoriasis tend to have more severe disease than patients with Type 2 psoriasis. Additionally, Type 1 disease has a strong genetic component. Patients with this type of psoriasis tend to have more relatives who have the disease than patients with late onset psoriasis (Langley et al., 2005).

Furthermore, a positive relationship between the incidence and prevalence of psoriasis and latitude has been observed. A study by Springate et al (2017) reported that the incidence of psoriasis increased by 6.5 cases per 100,000 for every degree increase in latitude and prevalence increased by 201 cases per 100,000 for every degree in latitude (Springate et al., 2017). The results from this study also showed that the mean incidence and prevalence of psoriasis was 144 and 2323 (per 100,00 cases), respectively, in South West England. Conversely, in Scotland, the mean incidence and prevalence of psoriasis was 174 and 3060 (per 100,00 cases), respectively (Springate et al., 2017). These results highlight the variation in the incidence and prevalence of psoriasis between north and south regions of the UK.

Psoriasis manifests in the form of plaques on the surface of the skin which appear red or pink in colour and have a coarse texture due to the presence of scales. These scales may give the plaques a silvery appearance (see Figure 1.1). Due to the clinical appearance of psoriasis the condition is often referred to as a papulosquamous skin disorder (Griffiths and Barker, 2007). Psoriasis Vulgaris, also known as chronic plaque psoriasis, is the most common type of the skin disease as it affects approximately 90% of patients (Griffiths et al., 2007). Chronic plaque psoriasis is characterised by the presence of distinctive plaques which can vary in size and degree of inflammation. These plaques can be irregular or oval in shape and typically occur on the extensor aspects of the elbows and knees, the lumbosacral area, the intergluteal cleft and scalp (Naldi and Gambini, 2007). Chronic plaque psoriasis may also present in the nails of patients, around 40-50% of patients show nail involvement (Griffiths et al., 2007). The most common clinical manifestation of psoriasis in the nail is known as ‘pitting’ whereby small serrations appear in the nail plate (Wozel, 2008). Nail involvement often occurs in patients suffering with psoriatic arthritis (Griffiths and Barker, 2007).

Figure 1.1 The distinctive psoriatic plaque. Note the white, flaky texture due to the presence of scales.



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During bouts of disease activity lesions may become more inflamed and coalesce resulting in a larger percentage of the skin being covered in plaques. This is commonly observed on the lower limbs and sacral region of the body (Lui and Mamelak, 2011). Psoriatic erythroderma is where more than 90% of the body is affected by the disease. Patients are frequently admitted to hospital for treatment when such a large percentage of their body is affected by the disease (Sheth, 2009). Other subtypes of psoriasis include guttate, flexural and pustular psoriasis, summarized in table 1.1.

Table 1.1 Clinical subtypes of psoriasis.

Type of Psoriasis	Features
Guttate	Guttate psoriasis is an acute form of the skin disease which occurs following streptococcal pharyngitis or tonsillitis (Lowes et al., 2007) This type of psoriasis accounts for approximately 2% of psoriasis cases (Langley et al., 2005) and is most common amongst children and young adults (Griffiths et al., 2007). Guttate psoriasis is distinguished by small papules which are often dispersed over large areas of the body, namely the torso, back and limbs (Lowes et al., 2007).
Flexural	Flexural psoriasis is characterised by plaques which are bright red in colour and are found in the folds of the skin, for example, the groin and natal cleft. The plaques are smooth in texture and do not appear scaly like those in typical chronic plaque psoriasis (Griffiths et al., 2007).
Pustular	Pustular psoriasis is commonly observed in adults. This type of psoriasis can be further subdivided into localised and generalised pustular psoriasis. Localised pustular psoriasis, also known as palmoplantar pustulosis, accounts for approximately 5% of psoriasis cases. Localised pustular psoriasis is typically observed on the palms of the hands and the soles of the feet (Tanaka et al., 2000). Generalised pustular psoriasis (also referred to as von Zumbusch psoriasis) is a rare form of the disease which tends to be most common among women and often occurs in individuals around the age of 40 (Griffiths and Barker, 2007). The plaques observed in this type of psoriasis are typically red in colour, appear inflamed and are studded with sterile pustules. These pustules amalgamate resulting in large areas of skin being affected. This type of psoriasis can be triggered by the sudden withdrawal of corticosteroids (Langley et al., 2005).

1.2 Psoriasis Pathogenesis

Early clinical studies have demonstrated the fundamental role of the immune system, more specifically T cells in the pathogenesis of psoriasis. Specific T cell responses require the activation of these cells through antigen presenting cells (APC's), such as dendritic cells (DC's) (Ghoreschi et al., 2007). The binding of a T cell to an APC is mediated via surface molecules. Leukocyte function associated antigen 1 (LFA-1) and CD2 on the T cell binds to intercellular adhesion molecule 1 (ICAM-1) and LFA on the APC. Subsequently, the T cell receptor binds to a short peptide which is presented by the major histocompatibility complex (MHC) on the APC; this process is known as signal 1. A T cell will only bind with a peptide that is specific for its receptor (Mehlis and Gordon, 2003). The last stage in the process of T cell activation is costimulation which is known as signal 2. The second signal is necessary to complete the activation of the T cell and it is supplied by the interaction of costimulatory molecules on the APC and the T cell. In the absence of the second signal (costimulation) the T cell will either become anergic (unresponsive) or undergo apoptosis (Bugeon and Dallman, 2000). Once they have become activated the T cells interact with endothelial cells and move out of the peripheral circulation (Griffiths, 2003). The T cells then migrate to the skin and accumulate around dermal blood vessels. This lymphocytic infiltrate primarily consists of CD4 T cells (Coimbra et al., 2012).

1.2.1 Th1 cells

Psoriasis is associated with an over expression proinflammatory cytokines produced by T helper 1 (Th1) cells and was therefore historically considered to be a Th1 disease (Arican et al., 2005). Th1 cytokines which have been observed in psoriatic lesions

include Interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), interleukin-2 (IL-2) and IL-12 (Schlaak et al., 1994). Additionally, previous work has reported significantly high levels of Th1 cytokines (including IFN-γ, TNF-α and IL-12) and proinflammatory cytokines (including IL-6, IL-8 and IL-18) in the serum of psoriasis patients. A significant correlation was also found between the serum levels of IFN-γ, IL-12, IL-17 and IL-18 and the severity of disease (Arican et al., 2005). The pattern of cytokine expression implies that Th1 cells may be responsible for mediating or maintaining disease (Coimbra et al., 2012).

The increase in Th1 cells is in part supported by IFN-γ which plays a vital role in the development of Th1 cell-mediated responses (Coimbra et al., 2012). This cytokine is secreted by Th1 cells, DC's and natural killer (NK) cells and is thought to play a role in the development of new psoriatic plaques (Yawalkar et al., 1998, Gaspari, 2006). IFN-γ is particularly important in the early stages of psoriasis as it increases the rate at which immune cells migrate into the skin and activates APC's. Additionally, IFN-γ inhibits the apoptosis of keratinocytes therefore partially contributing to the increased number of these cells in psoriatic lesions (Coimbra et al., 2012).

TNF-α, another cytokine of the Th1 pathway, increases the production of proinflammatory molecules such as IL-6 and IL-8 (Victor and Gottlieb, 2002). IL-6 mediates the activation of T cells and stimulates the proliferation of keratinocytes (Sehgal, 1990). IL-6 also has roles in regulating the immune response, haematopoiesis, the acute phase response and inflammation (Ishihara and Hirano, 2002). Increased levels of IL-8 have been found in psoriatic lesions. Various studies have indicated that this proinflammatory cytokine has a key role in the pathomechanism of psoriasis (Arican et al., 2005). Previous evidence has shown that IL-8 plays a vital role as a chemoattractant for the recruitment of neutrophils and T lymphocytes to the epidermis, suggesting that it has an important role in the development of psoriatic plaques. It has also been found that IL-8 is involved in

stimulating keratinocyte proliferation (Barker et al., 1991). In addition to increasing the production of proinflammatory cytokines, TNF-α also enhances the production of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), P-selectin and E-selectin (Victor and Gottlieb, 2002). It has been suggested that adhesion molecules, particularly E-selectin, are essential for the initial trafficking of T memory cells into psoriatic lesions (Wakita and Takigawa, 1994). Both TNF-α and IFN-γ increase the expression of ICAM-1, which in turn promotes the infiltration of T cells and other inflammatory molecules into the skin (Coimbra et al., 2012). The neutralisation of TNF-α has been applied in some psoriasis therapies (Chaudhari et al., 2001) which supports the idea that it has an important role in the development of the disease and is involved in keratinocyte proliferation (Coimbra et al., 2012).

1.2.2 Th17 cells

The Th1 subset of activated T cells is numerically the most dominant type of T cell within psoriatic lesions and has been the primary focus of the literature since the mid 1980's (Martin et al., 2013). More recently however, the focus has shifted toward Th17 cells which are a novel subtype of T cells expressing IL-17. It has been found that Th17 cells have a central role in the development of psoriasis (Quatresooz et al., 2012). It has been shown that there are significantly more Th17 cells in the dermis of psoriatic skin in comparison to that of healthy skin. It has also been reported that IL-17 mRNA increases with disease activity (Lowes et al., 2008). These findings suggest that Th17 cells may be proximal regulators of inflammation in psoriatic skin and therefore perhaps more attention should be given to Th17 cells as potential therapeutic targets (Lowes et al., 2008).

Th17 cells are $CD4^+$ effector T-helper cells that are distinct from the classic Th1 and

Th2 cell lineages. The role of these cells in the host defence system is to provide protection against fungi and extracellular bacteria (Zielinski et al., 2012). Th17 cells are activated by IL-23, IL-1β and IL-21. IL-23 in particular is up-regulated in psoriatic lesions as it is essential for the differentiation and survival of Th17 cells (Guttman-Yassky et al., 2008). It has been suggested that the IL-23/Th17 pathway, which is activated in psoriasis, is perhaps responsible for the distinct features of the disease, such as cellular infiltrates and increased production of proinflammatory cytokines (Wilson et al., 2007). Once activated, Th17 cells produce various inflammatory factors, including IL-17A, IL-17F and IL-22 (Martin et al., 2013). Il-17A and IL-17F act directly on keratinocytes in order to stimulate the production of various molecules which are known to be present in high levels in psoriatic lesions. These molecules include cytokines, β-defensins antimicrobial peptides (AMP's) and various chemokines (Guttman-Yassky et al., 2008). Additionally, psoriasis patients who are at an increased risk of cardiovascular events have been observed to have increased levels of circulating IL-17A-producing cells (Martin et al., 2013). IL-17 also stimulates the production of other cytokines and angiogenic factors. This results in naïve T cells becoming committed to the Th17 cell lineage which as a result generates a positive feedback loop for the Th17 inflammatory environment (Quatresooz et al., 2012). IL-22 also acts on keratinocytes to alter the maturation process of these cells and causes them proliferate much faster than normal. This then leads to the characteristic epidermal hyperplasia (acanthosis) observed in psoriatic lesions. Together IL-17 and IL-22 have a synergistic effect on the keratinocytes so they are resistant to microbial infection (Quatresooz et al., 2012).

The extraordinary results from clinical trials have confirmed the role of IL-17 in psoriasis. A correlation between changes in the IL-17 pathway and successful therapy as well as the observed effects of the inhibition of both IL-17A and the IL-17A receptor provide evidence for the central role of IL-17 in the disease (Martin et al., 2013). IL-17 inhibitors are currently in phase II clinical trials and it is thought that they will

become important in the treatment of psoriasis in the future. The aim in terms of treatment of this disease is to produce more targeted and efficacious therapies (Sauder and Sauder, 2013).

1.3 Treatment of psoriasis

There is currently a wide range of treatment options available to patients with psoriasis including topical creams, ultraviolet (UV) light therapy, systemic treatments and biologics. Topical agents tend to be the first choice of treatment for those with mild to moderate disease, as well as an adjunctive therapy for those with more severe involvement who have already been prescribed a systemic or biologic therapy (Kilic and Gul, 2010). Topical treatment options include: vitamin D analogues, topical corticosteroids, tar-based preparations, dithranol, salicyclic acid and topical retinoids (Mason et al., 2009). Emollients and moisturisers are used as supportive agents to topical treatments as they can help to reduce itching and scaling of the skin (Mason et al., 2009).

Moderate to severe psoriasis is usually treated with phototherapy, systemic therapies or biologic agents (Laws and Young, 2010). The two main types of prescribed phototherapy are narrow-band UVB and psoralen UVA (or PUVA). Narrow-band UVB is used to treat psoriasis which has not responded to topical treatments (Stern, 2007). A dermatologist will calculate how much UVB light a person's skin should be exposed to. Patients receiving this treatment attend a phototherapy unit, usually in a hospital Dermatology department or clinic, three times a week for four to six weeks. Previous studies in patients with psoriasis have compared two versus three times per week narrow-band UVB treatment and three versus five times per week (Cameron et al., 2002, Dawe et al., 1998, Hallaji et al., 2010). It was concluded from these studies that treatment three times per week was the most preferable regime

for the majority of patients (Cameron et al., 2002, Dawe et al., 1998, Hallaji et al., 2010). Although five times weekly treatment with narrow-band UVB clears psoriasis more rapidly, it is not sufficient to justify the extra exposures and higher UVB dose in a population of patients with a skin type of I to III (Dawe et al., 1998).

PUVA therapy is a combination of UVA light and a chemical known as psoralen which can be administered as a tablet or applied to the areas of skin being treated in the form of a gel or cream. Alternatively, it can be added to bath water to soak the whole body. The purpose of psoralen is to enhance the skin's sensitivity to the UVA light. PUVA is used to treat moderate to severe psoriasis which has not responded to topical agents or UVB therapy (Stern, 2007). Patients receiving PUVA are treated three times a week, for a period of 12 weeks (at least) (Koo and Nakamura, 2017).

Systemic treatments for psoriasis are prescribed to those with moderate to severe disease who have not responded to topical agents or UV therapy. The 3 most widely used systemic agents for psoriasis are Methotrexate, Ciclosporin and Acitretin (Lebwohl and Ali, 2001). Methotrexate is taken once a week either in the form of a tablet or an injection. Folic acid can be prescribed along with Methotrexate in order to help reduce nausea which can be caused by the Methotrexate (Lebwohl and Ali, 2001). Ciclosporin is an immunosuppressant which is taken daily in the form of an oral capsule (Griffiths, 1990). Acitretin is usually prescribed for severe plaque psoriasis, erythrodermic psoriasis and some cases of pustular psoriasis. It is usually taken on a daily basis in the form of an oral capsule. Acitretin is often used in rotation with other systemic treatments and in conjunction with UV therapy or topical agents (Hodulik and Zeichner, 2006). A dermatologist will determine the correct dosage and frequency of Acitretin for each individual patient. Fumaric acid esters are another form of systemic treatment, used primarily in individuals with moderate to severe psoriasis (Balasubramaniam et al., 2004). Generally, individuals start on a low dose of fumaric

acid esters (one tablet daily) and gradually increase their dosage in order to prevent side-effects, such as nausea, abdominal distension and diarrhoea (Wain et al., 2010). A more recent systemic treatment used in moderate to severe psoriasis is known as Apremilast, which is a phosphodiesterase-4 inhibitor (Schafer et al., 2010b). This drug is taken orally in the form of a tablet, twice daily. Apremilast is currently being used in patients who have failed to respond to or are intolerant to other systemic therapies (Poole and Ballantyne, 2014).

The introduction of biologic therapies has revolutionised the treatment of psoriasis. Unlike any other treatments for psoriasis, these agents are designed to target specific components of the immune system (Sivamani et al., 2010). Table 1.2 highlights the biologic agents available or those currently undergoing Phase III clinical trials for the treatment of psoriasis, along with the site of action and dosage/administration of each drug (Campa et al., 2016, Dong and Goldenberg, 2017).

Table 1.2 The biologic agents currently available or under development for the treatment of severe psoriasis.

Biologic agent	Site of Action	Dosage/administration
Adalimumab	TNF-α	Self-administered injection every other week
Infliximab	TNF-α	3 X 2hour infusions given in the first 6 weeks, then once every 8 weeks
Etanercept	TNF-α	Self-administered injection 1-2 times a week
Ustekinumab	IL-12 and IL-23	Taken by injection – initial doses at 0 and 4 weeks and every 12 weeks thereafter
Secukinumab	IL-17A	Self-administered injection for the first 4 weeks and monthly thereafter
Brodalumab	IL-17A	One subcutaneous injection at Weeks 0, 1 and 2 and one injection every two weeks thereafter (under review for FDA approval)
Ixekizumab	IL-17A	Two subcutaneous injections at Week 0, followed by one subcutaneous injection every two weeks for 12 weeks and then one maintenance injection every four weeks
Risankizumab	P19 subunit of IL-23	Subcutaneous injection at weeks 0, 4 and 16 (currently undergoing Phase III trials)
Guselkumab	P19 subunit of IL-23	Subcutaneous injection at weeks 0 and 4 and every 8 weeks thereafter (currently undergoing Phase III trials)
Tildrakizuman	P19 subunit of IL-23	Subcutaneous injection at weeks 0 and 4 and every 12 weeks thereafter (currently undergoing Phase III trials)

Other agents, currently under development for the treatment of psoriasis, include A3 adenosine receptor agonists and Janus kinase inhibitors, among others (Papp et al., 2016, Yiu and Warren, 2016).

1.4 Comorbidities

Psoriasis, like various other immune-mediated inflammatory diseases, is associated with a number of comorbidities. Physical comorbidities such as psoriatic arthritis, Crohn's disease and stroke are all prevalent in the psoriasis population (Kimball et al., 2010a). Psoriasis has also been associated with cardiovascular disease (CVD) and metabolic syndrome (which refers to the combination of cardiovascular risk determinants including obesity, dyslipidaemia, hypertension, glucose intolerance and insulin resistance (Bruce and Hanson, 2010)). The relationship between psoriasis and CVD has recently started to dominate the research regarding psoriasis and the systemic sequelae associated with it (Gottlieb et al., 2008). The relationship between psoriasis and physical comorbidities is linked with the chronic inflammatory nature of psoriasis itself (Alexandroff et al., 2009). It has therefore been proposed that psoriasis may be an independent risk factor for CVD. However, there is growing recognition of the importance of unhealthy behaviours (some of which are CVD risk factors) and their relationship with the onset and severity of psoriasis. This means that it could be the high incidence of these behaviours amongst psoriasis patients which is making them more susceptible to developing CVD (Martyn-Simmons et al., 2011) (see section 1.6 for more detail).

Psoriasis is associated with various psychological and social comorbidities. A number of studies have provided indubitable evidence that psoriasis patients experience symptoms of depression, anxiety and suicidal ideation (Fortune et al., 2000, Kurd et al., 2010). It has been reported that patients may also find it difficult to verbally express their emotions, particularly feelings of anger (Young, 2010). It is frequently

recognised that the stigma associated with visible skin lesions creates a strong psychological and social burden for patients. Psoriasis can impact on various aspects of a patient's life including their intimate relationships, social activities, work and emotional well-being (Kimball et al., 2010a). Psoriasis can also have a significant effect on a person's body image and self-confidence. The chronic nature of the disease, the alteration in physical appearance due to psoriatic lesions and the constant need for medical intervention are all contributing factors to the development of depression and suicidal thoughts in psoriasis patients (Devrimci-Ozguven et al., 2000). However, it is important to note that the severity of a person's depression is not always directly linked to the severity of their disease (Gupta and Gupta, 2003). It has been reported that the prevalence of depression in psoriasis patients is significantly greater than in patients with other dermatological disorders which are known to impair physical appearance. Such disorders include atopic dermatitis, alopecia areata and non-cystic facial acne. The higher incidence of depression in psoriasis patients is also associated with an increased suicide risk (Young, 2010).

Numerous studies have supported the associated between depression, suicide ideation and psoriasis. One study by Gupta et al involved 217 psoriasis patients who completed the Carroll Rating Scale for Depression (a self-rated scale consisting of 52 items). This study found that almost 10% of these patients expressed a death wish whilst 5.5% of patients reported having suicidal thoughts at the time of the study (Gupta et al., 1993). Also in a later study it was found that suicidal ideation was more prevalent in patients with severe psoriasis (greater than 30% of skin surface area affected) compared with general medical in-patients (Gupta, 1998). The depressive symptoms and suicidal ideation a patient may experience in response to psoriasis may provide an explanation for the immobilising effects of the disease (Devrimci-Ozguven et al., 2000).

In spite of this evidence, a recent study by Egeberg et al (2016) found limited evidence to suggest an increased risk of self-harm and non-fatal suicide attempts in patients with psoriasis (Egeberg et al., 2016). The cohort in this study comprised 408,663 Danish patients, aged 18 or over, with mild or severe psoriasis. There was no increased risk of self-harm or suicide attempts in patients with mild psoriasis, although this risk was significantly increased in severe psoriasis. There was no increased risk of suicides in mild or severe psoriasis (Egeberg et al., 2016).

1.5 Psoriasis assessment challenges

1.5.1 Overview of this section

A wide range of outcome measures are used to evaluate the severity of psoriasis and its response to treatment, both clinically and in research trials (Ashcroft et al., 1999). However, choosing a measurement tools and how to utilise the data can sometimes be challenging. Additionally, the factors which contribute to 'severe' disease may vary depending on the assessor. Patients, clinicians, clinical researchers and healthcare organisations may all focus on various aspects of the disease, which therefore leads to different ways of defining 'severe' psoriasis (Finlay, 2005). For example, from the patient's perspective, they may consider their psoriasis to be severe if it causes them embarrassment or anxiety or if it affects their daily activities (Finlay, 2005). The impact of psoriatic lesions can often vary significantly among different individuals (Feldman and Krueger, 2005). On the other hand, from the clinician's perspective, they may consider a patient's psoriasis to be severe if it is very widespread or if it responds poorly to long-term or intensive treatment (Finlay, 2005).

It is now recognised that patient-reported outcome measures are equally as important as assessments made by a clinician. These measures support treatment decision

making and help to identify patient coping strategies (Kitchen et al., 2015). The National Health Service (NHS) now states that a key area of improvement is to focus on enhancing quality of life for people with long-term conditions, which is particularly relevant to patients with psoriasis (Kitchen et al., 2015).

This section will focus on the measurement tools used to assess both the current level of disease presentation and the impact of psoriasis on quality of life, along with the challenges both clinicians and researchers face when putting these tools into practice.

1.5.2 Current level of presentation: psoriasis area severity index

The psoriasis area severity index (PASI), which was developed by Fredricksson and Pettersson in 1978, is the most common method used to gauge the severity of psoriasis (Langley and Ellis, 2004). The PASI is a physical measure of disease severity which takes into account the percentage of skin surface area affected by psoriasis. This percentage is formulated based on scores assigned to the severity of: erythema (redness of the skin), the thickening and hardening of psoriatic plaques (induration) and the desquamation of plaques (Fredriksson and Pettersson, 1978, Kirby et al., 2000). The severity of psoriasis is assessed in this way on four main areas of the body including the head, the trunk of the body and the upper and lower limbs (Fredriksson and Pettersson, 1978, Kirby et al., 2000, Langley and Ellis, 2004). Using this information a PASI is calculated in order to provide an indication of psoriasis severity; the score is a single integer and may be anything between 0 and 72 (Fredriksson and Pettersson, 1978, Langley and Ellis, 2004). According to the NICE guidelines a PASI of 10 or more indicates severe psoriasis. See section 3.5.2 for more information on how the PASI is calculated.

The PASI is a measure of current disease activity which means that it provides a ‘snap-shot’ of a person’s psoriasis. An advantage of the PASI is that it is sensitive to change which means that changes in PASI do reflect disease improvement or exacerbation (Finlay, 2005). This also means that PASI is a useful outcome measure when assessing a patient’s response to a particular treatment. A 50%, 75% or 90% reduction in PASI, in comparison to baseline, is considered to be a clinically significant endpoint (Sterry et al., 2004). The PASI is thought to be the ‘gold standard’ measure of plaque severity in clinical trials (Reich and Griffiths, 2008). On the other hand, the use of the PASI in clinical practice has been criticised for being time-consuming

(Finlay, 2005, Chow et al., 2015), difficult to interpret (Chow et al., 2015) and prone to error in the calculation of the overall PASI (Chalmers, 2015). There are also concerns regarding interrater reliability due to lack of validation (Schmitt and Wozel, 2005).

Another disadvantage of the PASI tool is that it does not reflect the course of disease as it provides only a 'snap-shot' of physical severity (Schmitt and Wozel, 2005). This can be frustrating for a patient as they may have a flare-up of psoriasis in between their clinic appointments which is not seen by the clinician. Additionally, the PASI does not take into account changes in disease presentation in response to other factors such as stress or infection (Schafer et al., 2010a). The PASI also provides no indication of former therapies (Schmitt and Wozel, 2005).

It is important to recognise that a patient's PASI does not always predict the impact of psoriasis on their quality of life (Finlay, 2005, Reich and Griffiths, 2008). There is often a significant difference between the physical presentation of psoriasis and the impact it has on quality of life. The impact of psoriasis on quality of life has previously been underestimated. There is evidence that psoriasis has a negative influence on important aspects of patient's lives to an extent comparable to that of other medical conditions including heart disease, diabetes and depression (Reich and Griffiths, 2008). Hence, more recently self-report quality of life measures are now being used in conjunction with the PASI and other objective measures of disease presentation, in order to monitor treatment response (Schafer et al., 2010a). Stronger correlations between PASI and quality of life measures have been observed when the percentage reduction in the PASI is greater than 50%. Studies have shown that patients who achieved a ≥75% reduction in their PASI indicated a greater improvement in their quality of life (Schafer et al., 2010a, Mattei et al., 2014, Reich and Griffiths, 2008). However, as a ≥75% reduction in PASI is not always achieved and the impact of

psoriasis on quality of life is unique to each individual, it is important to assess PASI and quality of life in parallel. Regulatory authorities expect the Dermatology Life Quality Index (DLQI) to reflect the impact of disease.

1.5.3 Self-administered psoriasis area severity index

The self-administered PASI (SAPASI) is a structured instrument which allows the patient to report the physical severity of their own disease. The SAPASI consists of silhouettes of a body (both anterior and posterior) for patients to shade in the areas where their psoriasis is present (Fleischer et al., 1994). Patients are also provided with 3 visual analogue scales for recording the erythema, induration and scaliness of an average psoriatic lesion. A third person then translates the patient's ratings into a score which reflects the intensity and extent scales of the PASI (Schmitt and Wozel, 2005).

A disadvantage of the SAPASI is that there is no 'gold standard,' however SAPASI measurements have been compared with PASI (Ashcroft et al., 1999). Previous studies have observed significant correlations and high interrater reliability between PASI and SAPASI (Feldman et al., 1996, Ashcroft et al., 1999, Henseler and Schmitt-Rau, 2008). The SAPASI can therefore act as a reliable measure of the physical severity of psoriasis in clinical trials if the assessment cannot be performed by a clinician (Schmitt and Wozel, 2005).

The SAPASI has also been found to correlate well with the health-related quality of life measure, DLQI (Wade et al., 2016).

1.5.4 Impact of psoriasis on quality of life: dermatology life quality index

As mentioned in section 1.5.2 the psychosocial impact of psoriasis on patients is frequently overlooked, despite the fact that numerous studies have highlighted a negative relationship between psoriasis and health-related quality of life (Lewis and Finlay, 2005). Psoriasis is a distressing disease which can impose on a patient's physical, social and emotional well-being (Meyer et al., 2010). However, the distress experienced by a psoriasis patient may be linked to cognitive functioning rather than the physician's rating of disease severity. It is therefore crucial that the impact of the disease on a patient's quality of life is monitored as a part of their treatment regime using patient-centred measures (Sampogna et al., 2004). To date various instruments have been generated to evaluate quality of life, such as the Health assessment questionnaire (HAQ). However, the most widely used tool for assessing quality of life in relation to skin disease is the DLQI (Reich and Griffiths, 2008).

The DLQI was developed by Finlay and Khan in order to assess the impact of skin diseases on a person's quality of life (Finlay and Khan, 1994). The DLQI is a self-reported questionnaire which evaluates the impact of a skin disease on a patient's quality of life over the course of seven days (Lin et al., 2011). The questionnaire consists of 10 questions in total, each with a possible four answers for the patient to choose from. The questions cover a range of topics including: symptoms and feelings, daily activities, occupation or education, leisure, relationships and treatment. A score out of 30 is generated upon completion of the questionnaire; 0 indicating that psoriasis has no effect on quality of life and 30 indicating that psoriasis has a significant effect on quality of life (Gniadecki et al., 2012, Reich and Griffiths, 2008). According to the NICE guidelines a DLQI score greater than 10 indicates that psoriasis is having a considerable impact on a person's quality of life. The DLQI is the most common tool

used to measure the health-related quality of life of psoriasis patients internationally (Blome et al., 2010).

The DLQI has been utilised extensively in psoriasis research and test-retest reliability has been shown to be high in numerous studies (Basra et al., 2008, Simpson et al., 2015). The DLQI was an integral part of the assessment of new systemic therapies (Finlay, 2005). A major advantage of the DLQI is that it has been found to detect changes in SAPASI as well as small significant changes over time (Mazzotti et al., 2003, Finlay, 2005, Shikiar et al., 2006). In a consensus statement on therapies for psoriasis it was concluded that quality of life measures should be taken into consideration when deciding on an appropriate treatment for a patient (Callen et al., 2003, Finlay, 2005). However, a concern with using the DLQI in the clinic is that little is known about how the quality of life scores are interpreted and how they influence treatment choice. For example, a 50% or 75% reduction in DLQI score could be used an outcome measure of treatment. Although, what should be considered, from the patient's point of view is that their quality of life has improved and is at a level which means that they are unaffected (DLQI score of 0-1) or at a level where their psoriasis has only a small effect (DLQI score of 2-5) (Finlay, 2005).

The DLQI has been criticised for not fully capturing the effect of skin disease on people's emotions and mental health (Badia et al., 1999). The implication of this is that the DLQI may lack conceptual validity, particularly in patients with minor dermatological conditions or in conditions which have a significant impact on mental health (Both et al., 2007). A further appraisal of the DLQI concluded that the some of the items on the questionnaire did not seem to group logically together (Nijsten et al., 2006). It was also observed that a large proportion of the items on the DLQI provoked very different responses across age and gender (Nijsten et al., 2006, Both et al., 2007). This perhaps suggests that more care should be taken when interpreting individual DLQI scores and more attention should be paid to the individual items on

the questionnaire. The latter is particularly important since the DLQI covers various aspects of a person's life. For example, this means that a low DLQI score could lead a clinician to believe that a patient is rather unaffected by their psoriasis when in fact, they have scored highly on one item which means that their psoriasis is having a significant impact on one aspect of their life.

In summary, as well as being used as a measure of health-related quality of life prior to and after treatment, the DLQI has also become a key element of current definitions of disease severity in psoriasis (Both et al., 2007). The informative value of clinical research in psoriasis is enhanced by the use of the DLQI.

1.5.5 Simplified psoriasis index

The simplified psoriasis index (SPI) is a summary measure of psoriasis which is composed of 3 individual components: current severity (SPI-s), psychosocial impact (SPI-p) and disease history and interventions (SPI-i) (Chularojanamontri et al., 2013). Each component of the SPI is assigned an individual score. This tool derives from the Salford Psoriasis Index, which was developed in the late 1990's and was designed to provide a succinct overview of psoriasis severity (Kirby et al., 2000). Two forms of the SPI are available, one of which is intended for use by health professionals (proSPI) and one which is for self-assessment by patients (saSPI). The two versions of the SPI are very similar apart from the simplification of the language used in the self-assessed SPI. (Chularojanamontri et al., 2013).

The SPI contains a composite severity score (SPI-s) which eliminates the need for a PASI. The SPI-s comprises 2 parts: part (a) provides a list of 10 areas of the body and asks patients to rate psoriatic involvement of the skin using a 3-point scale (absent=0, noticeable but still plenty of unaffected skin=0.5 and extensive

involvement=1). Part (b) of the SPI-s asks patients to rate, on a 6-point scale (0-5), the overall state of their psoriasis. This score dispenses the need to assess erythema, scale and plaque thickness separately (Chularojanamontri et al., 2013).

The SPI-p score coverts a 10 centimetre visual analogue rating to the nearest integer, ranging from 0-10, with 0 indicating that psoriasis has no psychosocial impact and 10 indicating that psoriasis has a significant psychosocial impact on the individual (Chularojanamontri et al., 2013). Finally, the SPI-i score consists of 10 items, 4 of which cover disease course and 6 which cover previous interventions. The maximum score that can be obtained is 10, however, this section of the SPI was designed to be flexible in order to accommodate variations in practice and the introduction of new therapeutic agents (Chularojanamontri et al., 2013). More details regarding the scoring of the individual components of the SPI can be found in section 3.5.2.

An advantage of the SPI is that it is easily understandable and time efficient. Strong intrarater and interrater reliability was also demonstrated with the SPI (Chalmers, 2015). Additionally the SPI-s, which assesses physical severity, divides the body surface into 10 unequal areas which means that more prominence is given to body parts where psoriasis is likely to have a significant impact on self-esteem or normal functioning (Chularojanamontri et al., 2013). This information cannot be obtained from the PASI.

Another advantage of the SPI is that it gathers information regarding both the psychosocial impact of psoriasis (SPI-p) and the historical course of disease and interventions. Therefore, providing a much more informative score than current severity alone (Chularojanamontri et al., 2013). The SPI-i in particular provides a useful additional dimension which is unable to be captured by the SPI-s, the SPI-p, the PASI or DLQI. The SPI-i is also a flexible component of the SPI which is structured to accommodate future changes (Chularojanamontri et al., 2013).

A minor criticism of the SPI is that the psychosocial burden of psoriasis is assessed using a single item, which may not depict the full impact of psoriasis on a patient's quality of life (Kitchen et al., 2015). Hence the use of additional measures when assessing the overall severity of a person's psoriasis may be very important.

1.5.6 Summary

Given that psoriasis can affect people very differently it can be concluded that disease severity should be considered on a case-by-case basis (Finlay, 2005). All of the instruments described above are measures of psoriasis severity (Finlay, 2005), however they should be used in conjunction with each other in order to assess current presentation, disease history and impact on quality of life in order to ensure that the assessor has a complete overview of a person's disease. A patient with psoriasis will likely experience changes in symptom severity and quality of life over the course the disease (Reich and Griffiths, 2008), however the PASI and DLQI may not capture these changes are they only provide 'snap-shot' measures. Hence, the SPI can provide a more detailed overview of disease and treatment history.

1.6 Psoriasis and CVD

1.6.1 Development of CVD

CVD, including myocardial infarction, stroke and heart failure is the leading cause of death in the developed world. The primary cause of CVD is atherosclerosis. There are a number of risk factors which increase a person's likelihood of developing atherosclerosis, for example high blood cholesterol, obesity, smoking lack of exercise, dyslipidaemia and hypertension (Scott, 2004).

The formation of an atherosclerotic lesion takes time and there are various cellular and molecular processes involved. Initially, a low-density lipoprotein (LDL) molecule is trapped in the sub-endothelial space of the vessel where it undergoes oxidation. The oxidised LDL is then engorged by macrophages which become activated leading to a state of chronic inflammation (Scott, 2004). Subsequently, proinflammatory cytokines and chemokines promote the expression of adhesion molecules, such as E-selectin. Leukocytes attach to these adhesion molecules which causes them to move out of the bloodstream and roll along the surface of the endothelial cells. The adhesion molecules leave the blood at the endothelial cell tight junctions. Smooth muscle cells are then recruited and stimulated by growth factors to proliferate and secrete collagen. Over time the fatty- fibrous atherosclerotic lesion develops (Scott, 2004).

There is now a growing body of evidence which suggests that psoriasis is associated with an increased risk of atherosclerotic disease (Alexandroff et al., 2009). According to a prospective population-based cohort study by Gelfand et al (2006), the most robust association exists between psoriasis and myocardial infarction. The aim of this study was to compare the outcomes amongst psoriatic patients and non-psoriatic

patients, the main outcome measure being myocardial infarction. The results from this study showed that psoriasis patients had an increased relative risk of myocardial infarction in comparison with matched controls. Additionally, the relative risk appeared to be greater in young individuals with severe psoriasis (Gelfand et al., 2006). Another study by Mehta et al (2010) reported a 57% increased risk of cardiovascular mortality in patients with severe psoriasis. This increased risk was independent of traditional CVD risk factors (Mehta et al., 2009).

In contrast, a study by Martyn-Simmons et al (2011) assessed preclinical CVD using flow-mediated brachial artery dilatation, which measures endothelium dysfunction, as well as hs-CRP, a serological marker of atherosclerosis (Martyn-Simmons et al., 2011). The results from this study revealed no significant difference in endothelial dysfunction between patients with psoriasis and healthy controls. However, levels of hs-CRP were significantly elevated in the psoriasis group. These results suggest that psoriasis itself is not an independent risk factor for CVD and elevated hs-CRP could be independent of atheroma risk (Martyn-Simmons et al., 2011).

It has also been observed that young psoriasis patients have significantly increased arterial stiffness and impaired endothelial function. However, the mechanism of vascular dysfunction and how it enhances the risk of CVD is unclear (Yiu et al., 2011). One study by Yiu et al (2011) found that psoriasis patients had significantly increased arterial stiffness however, there was no significant difference in vascular endothelial dysfunction between psoriasis patients and age and sex-matched controls (Yiu et al., 2011).

On the other hand, a study by Gisondi et al (2008) assessed arterial stiffness by carotid-femoral and carotid-radial pulse wave velocity (PWV). This study found that psoriasis patients had increased arterial stiffness compared to patients with other skin

diseases. It was concluded that moderate to severe chronic plaque psoriasis may be independently associated with increased arterial stiffness (Gisondi et al., 2008b). Furthermore, a study involving 3236 psoriasis patients and 2500 controls found a higher prevalence of ischemic heart disease in those patients with psoriasis after controlling for variables such as, diabetes mellitus, hypertension, dyslipidaemia and smoking. A higher prevalence of cerebrovascular and peripheral vascular diseases was also found in patients with psoriasis. It was concluded from this study that there is a definite association between psoriasis and atherosclerosis (Prodanovich et al., 2009).

Additionally, a recent study by Parisi et al (2015) proposed that patients with psoriasis have an increased prevalence of comorbidities associated with CVD. The results from this study showed that neither psoriasis nor severe psoriasis was significantly associated with the short to medium term risk (three to five years) of major cardiovascular events, when taking other CVD risk factors into consideration (Parisi et al., 2015). However, there was a higher prevalence of CVD risk factors in patients with psoriasis compared to healthy controls. This study also reported that the risk of a major cardiovascular event was 36% higher in patients with psoriasis who had inflammatory arthritis compared with those who did not. This study concluded that patients with inflammatory arthritis are at increased risk of CVD and therefore, this could be an additional reason to try to help minimise the patient's cumulative inflammatory burden (Parisi et al., 2015).

1.6.2 Mechanisms underlying the link between psoriasis and CVD

1.6.2.1 Inflammation

The inflammatory component of psoriasis may also elucidate its association with CVD. It has been shown that the levels of platelet-activating factor (PAF) are significantly increased in patients with psoriasis (Mallbris et al., 2004). PAF is an inflammatory mediator which plays a role in cardiovascular function (Montrucchio et al., 2000). The increased levels of PAF in psoriasis patients appear to correlate with the severity of disease. It has also been proposed that PAF plays a role in the initiation and maintenance of atherosclerosis. The increased activation of platelets in severe psoriasis could therefore be considered as a major contributor to the development of CVD (Mallbris et al., 2004).

Additionally, a number of other proinflammatory molecules such as, TNF-α and IL-17 have been implicated in the pathogenesis of psoriasis and CVD (Laws et al., unpublished) Inflammation is also a common component of both psoriasis and some of the risk factors associated with CVD, such as obesity. A growing body of evidence supports the anti-inflammatory effects of physical exercise independent of fat loss. It has been shown that physical activity can reduce the levels of TNF-α (Wilson et al., 2012). Although, it remains unknown as to whether changes in TNF- α concentration as a result of physical activity could translate into meaningful clinical improvements in psoriatic lesions or reductions in the risk of comorbidities. However, the use of TNF-α antagonists for the treatment of inflammatory driven diseases, including psoriasis, is becoming more common and provides circumstantial evidence that higher levels of physical activity could decrease the risk of CVD in psoriasis patients (Melnikova, 2009).

Furthermore, it is important to know that there is a relationship between distress and inflammation. Currently, there is no definitive link between the two however, stress does interact with the immune system and can have both short and long-term effects

1.6.2.2. Adhesion molecules

As mentioned above there is an increased expression of vascular adhesion molecules, including E-selectin and ICAM-1, in immune-mediated inflammatory diseases like psoriasis and atherosclerosis. A recent study by Laws et al revealed that the plasma levels of soluble E-selectin (sE-selectin; which has been previously identified as a biomarker for CVD) are also increased in patients with chronic plaque psoriasis. The plasma levels of this vascular adhesion molecule were shown to correlate with PASI independently from the conventional risk factors of CVD (Laws et al., unpublished). Furthermore, increased levels of ICAM-1 are associated with the metabolic syndrome and the development of CVD (Wilson et al., 2012). Evidence has shown that chronic exercise training reduced the expression of these adhesion molecules in an animal model (Yang and Chen, 2003).

1.6.2.3 Serum lipids

It has been suggested that hyperlipidemia and alterations in fatty acid composition are linked to the severity of psoriasis. Increased levels of oxidised low-density lipoprotein (LDL) cholesterol have been found in psoriatic lesions (Solak Tekin et al., 2007). Elevated levels of lipids and lipoproteins in the serum are well-known risk factors for CVD. Therefore, altered lipid profiles in psoriasis patients may increase their risk of developing CVD or cardiovascular-related events (Mallbris et al., 2004). Also, hyperlipidemia is a primary trigger for atherosclerosis. However, there is uncertainty as to whether the treatment of hyperlipidemia in psoriasis patients results

in the improvement of psoriasis symptoms (Ghazizadeh et al., 2011). Physical activity can help to reduce total cholesterol, LDL cholesterol and oxidation of lipids in the blood (Vasankari et al., 1998). However, more work needs to be done in regards to reducing the CVD risk in psoriasis patients.

1.6.3 Psoriasis as an independent risk factor for cardiovascular events

The authors of a US study observed that 43% of psoriasis patients (out of a total of 753) had some form of coronary artery disease, myocardial infarction, hypertension, congestive heart failure or cardiomyopathy (Pearce et al., 2005). Overall, a 14.3% greater prevalence of cardiovascular events were reported in patients with psoriasis in comparison to the general US population, even after controlling for confounding factors (such as age and sex) (Pearce et al., 2005). The higher prevalence of heart disease in patients with psoriasis has also been shown to be independent of BMI in some studies (González-Gay et al., 2012, Cohen et al., 2008). In one study, it was found that obesity was not an independent risk factor for acute myocardial infarction (González-Gay et al., 2012). In another study heart disease was reported in 14.2% of psoriasis patients compared with 7.1% of non-psoriatic controls (Cohen et al., 2008). This study used multivariate models of analysis which adjusted for various confounding factors including, age, gender and smoking status of patients. It was found that psoriasis was independently associated with ischemic heart disease (Cohen et al., 2008).

In another study, Kimball et al (2010) used the Framingham risk equation to calculate an estimate of the 10- year risk of coronary heart disease and stroke in 1519 patients with moderate to severe psoriasis. It was found that patients with a PASI (see methods section for more detail) between 10 and 20 had a 12.3% risk of coronary heart disease and an 8.3% risk of stroke. Patients with a PASI greater than 20 had a 12.2% risk of coronary heart disease and an 8.7% risk of stroke. It was concluded that, although the cardiovascular risk did not vary greatly according to the PASI, the level of risk was significantly higher than the general population in both groups (Kimball et al., 2010b).

It has also been suggested that the severity of psoriasis could influence the level of risk of cardiovascular events. Mallbris et al (2004) demonstrated that patients with severe psoriasis who required hospital admission for their disease (inpatients) had a higher risk of CVD mortality in comparison to outpatients with a considerably milder form of disease and the general population. Severe psoriasis was characterised by a PASI greater than or equal to 10. This study also revealed that the increased risk of CVD mortality was more distinct in patients who were hospitalised at a young age and those who were admitted to hospital on multiple occasions (Mallbris et al., 2004). This evidence supports the idea that the association between psoriasis CVD is linked to disease severity and age of onset.

1.6.4 Psoriasis as a contributing factor to CVD as opposed to an independent risk factor

The psychological and social effects of psoriasis could provide another explanation for the relationship between the disease and an increased risk of various cardiovascular events. It has been established that psoriasis is associated with known cardiovascular risks, namely smoking, obesity, hyperlipidaemia, diabetes, hypertension and the metabolic syndrome (Tablazon et al., 2013). It has been proposed that psoriasis patients may have an increased risk of cardiovascular events due to the higher prevalence of obesity amongst patients. The study by Kimball et al found that approximately 50% of the study population had a BMI greater than or equal to 30. However, the prevalence of obesity in the general population in the US in 2005 and 2006 was approximately 30%. The Framingham risk score used in this study does control for confounding factors related to obesity, such as cholesterol and hypertension however, it does not directly control for BMI (Kimball et al., 2010b). A case-control pilot study of 65 psoriasis patients and 52 controls also found that the control subjects had an average BMI of 25.67 whilst psoriasis patients had an average

of 27.72 (Tablazon et al., 2013).

The psychological impact of psoriasis itself could also explain why patients are at a higher risk of developing cardiovascular diseases. The consequences of psoriasis on patients' quality of life have been well documented. It has been observed that patients with psoriasis have high levels of anxiety, depression and worry (Richards et al., 2003) and in some case, they may experience suicidal ideation (Gupta et al., 1993). Additionally, people may feel embarrassed about their physical appearance and have low self-esteem. It has been established that the clinical severity of psoriasis is not a reliable measure of the burden of the disease and therefore, a psychological intervention is necessary (Kirby et al., 2001, Fortune et al., 2005). A study by Fortune et al (2002) showed that a cognitive-behavioural intervention, in conjunction with standard treatment for psoriasis, significantly reduced levels of anxiety and depression (Fortune et al., 2002).

It is well-established that psoriasis is associated with significant physical, psychological, social and economic burden, however, it has been proposed that the cumulative effect of this burden may result in failure to achieve 'full life potential' in some patients (Kimball et al., 2010a). It has been hypothesised the cumulative life course impairment (CLCI) in psoriasis results from interactions between the burden of stigmatisation and rejection, the physical and psychological comorbidities associated with the disease and coping strategies and other external factors (such as social support from family members, friends, colleagues and healthcare professionals) (Kimball et al., 2010a). For example, in patients with limited social support and ineffective coping mechanisms even a small burden may result in significant impairment. On the other hand, this effect may be less prominent in patients with a strong support network and effective coping strategies, even if the burden of severity is large (Kimball et al., 2010a). Indeed, the interaction of these components will vary throughout a patient's life, meaning that the risk or degree of

cumulative impairment will also change. Kimball et al (2010) proposed that, in order to accurately assess long-term or cumulative impairment, each of the key contributors must be taken into account. Given that the concept of CLCI is fairly new and very complex, further longitudinal research is needed to determine the mechanisms of impairment and how to reduce impairment with effective interventions (Warren et al., 2011).

As discussed above, one of the key components of CLCI in psoriasis is coping strategies; research has shown that one of the ways in which patients with psoriasis deal with the disease is through avoidance coping (Fortune et al., 1997b). This is where individuals avoid public places or situations where they feel they will be stigmatised on the basis of their skin (Fortune et al., 1997b). In a study by Fortune et al (1997), it was observed that avoidance coping behaviour was independent of the physical manifestations of psoriasis (Fortune et al., 1997b), which may imply that thoughts related to stigmatisation and rejection could be influencing such behaviour (Griffiths and Richards, 2001). This means that patients with psoriasis are anticipating negative experiences and rejection when they do not know that this will happen. The maintenance of such behaviour may contribute to low grade persistent stress which is thought to influence the course of disease (Griffiths and Richards, 2001). In addition, avoidance coping may also lead to decreased adherence to therapy, which in turn can exacerbate psoriasis (Kleyn et al., 2009). It has been reported that social avoidance is higher in patients with psoriasis than in patients with other skin diseases, including atopic dermatitis, acne and vitiligo (Stangier et al., 2003).

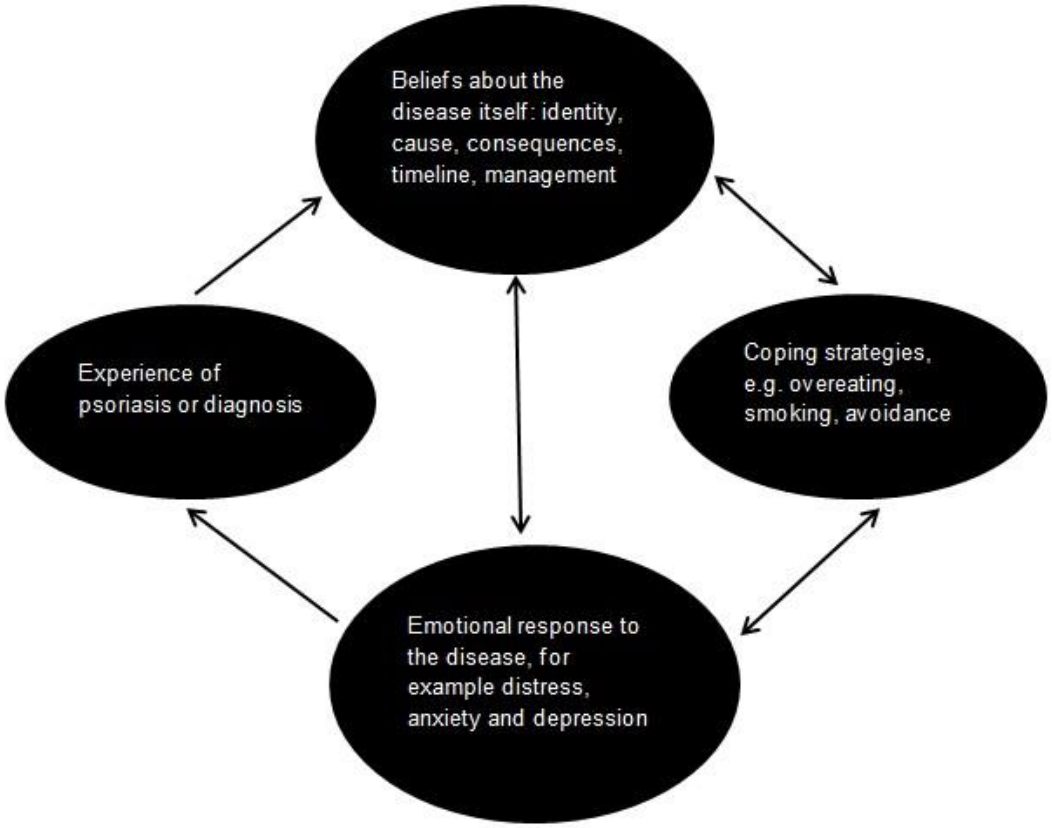
Psoriasis patients may also develop unhealthy behaviours such as, poor eating habits, excessive alcohol consumption or smoking as a way of coping with their disease. Patients may also avoid physical activity due to the physical symptoms of psoriasis such as itching, skin shedding or discomfort or perhaps due to stigmatisation or fear of rejection (Richards et al., 2001, Wahl et al., 2002). Some studies have

focused specifically on looking at the exercise patterns of psoriasis patients. A study by Al-Mazeedi et al showed that psoriasis impacts on levels of physical activity. It was found that physical activities were affected in more than 50% of patients who took part in the study (330 in total). This study also found that the severity of a person's condition, as measured by the PASI, correlated with physical activity (Al-Mazeedi et al., 2006). However, a key limitation with many of these studies is that they focus on a specific group of psoriasis patients, such as those who have been hospitalised for their disease. Additionally, patients who engage in unhealthy behaviours, such as smoking and alcohol consumption are more likely to be admitted to hospital. Therefore, these studies are limited by selection bias (Neimann et al., 2006). In addition, many of these studies do not take into account individual risk factors which may be independently associated with psoriasis (Neimann et al., 2006).

These unhealthy behaviours could all lead to an increase in body weight and the development of the metabolic syndrome, all of which are predisposing factors for CVD (Neimann et al., 2006). The symptoms of psoriasis can leave patients feeling embarrassed about their physical appearance resulting in low self-esteem. Consequently, this can lead to reduced social interaction, symptoms of depression (as mentioned above) and perhaps even the development of other comorbidities Figure 2 summarises the ways in which psoriasis patients may respond to their disease.

Figure 1.2 A summary of Leventhal's common sense model adapted for psoriasis (Diefenbach and Leventhal, 1996).

This diagram emphasises the different ways in which individuals may respond to their illness. Avoidance of physical activity may be an individual's coping strategy. Alternatively, the patient's personal beliefs about their disease or their emotional response to their disease or even the physical symptoms of disease could result in avoidance of physical activity.



1.6.5 Screening for cardiovascular events

1.6.5.1 Pulse Wave Velocity

Many studies have shown that arterial stiffness is a surrogate marker of CVD (Vlachopoulos et al., 2010, Van Bortel et al., 2012). PWV is 'the velocity of the pulse wave travelling the distance between two sites of the arterial system in a certain transit time' (Huybrechts et al., 2011, Laurent et al., 2006). When the aortic wall becomes rigid the velocity in the aorta increases, therefore the higher the PWV value, the more rigid the aorta is. Carotid-femoral PWV has been established as the 'gold-standard' assessment for arterial stiffness (Laurent et al., 2006).

The measurement of PWV therefore comprises two components: the transit time or time delay of the arterial pulse along the arterial pathway and the distance travelled between the two measurement sites (Huybrechts et al., 2011). There is a lack of standardisation when it comes to measuring the distance between the two sites. This is important as even small variations in the distance measurements can generate different PWV values (Van Bortel et al., 2012). An advantage of the PWV measurement is that it is non-invasive. However, this also means that distances are usually taken from measurements on the body surface area using a device such as a tape measure whilst the patient is in the supine position. There is no consensus on the most efficient way to measure this distance in the case of carotid-femoral PWV (Huybrechts et al., 2011). Some studies use the direct distance between the carotid and femoral measurement sites (Asmar et al., 1995). Alternatively, some studies subtract the distance from the sternal notch to the site of the carotid artery from the total distance between the carotid and femoral measurement sites (Blacher et al., 1999) or from the distance from the sternal notch to the site of the femoral artery (Weber et al., 2009). All of these methods aim to provide an estimation of the 'real' length travelled by the pulse wave (Huybrechts et al., 2011). An example of a method

which can be used to measure the ‘real’ distance travelled is magnetic resonance imaging (MRI), however this method is time-consuming and more expensive. A 2011 study compared the ‘real’ length travelled by the pulse wave to tape measurements. It was found that the direct distance between the carotid artery and the femoral artery (multiplied by 0.8), which was gauged using a tape measure, yielded the strongest agreement with the MRI measurements. A scaling factor of 0.8 was used to convert the direct carotid to femoral distance into the ‘real’ travelled distance. (Huybrechts et al., 2011). This scaling factor was derived from previous studies (Weber et al., 2009).

The transit time, which is the other component of the PWV measurement, can be measured accurately as the time difference between two characteristic points on carotid and femoral waveforms (The Reference Values for Arterial Stiffness, 2010). The characteristic points chosen are dependent on the type of waveform, for example flow pressure or diameter distension as well as the algorithm used for its detection. The two most common algorithms used for the detection of the waveform are: the intersecting tangent algorithm and the point of maximal upstroke during systole. The application of different algorithms on the same waveforms can result in differences in PWV values (The Reference Values for Arterial Stiffness, 2010). The type of algorithm used will vary according to which system is being used to measure PWV. Two of the most common systems used are the Sphygmocor system (which uses the intersecting tangent algorithm) and the Complior system (which uses the point of maximal upstroke during systole) (The Reference Values for Arterial Stiffness, 2010, Millasseau et al., 2005). Another system which is now being used to measure PWV is the TensioMed Arteriograph which enables the recording and analysing of arterial pulse waves. The TensioMed software is windows-based software consisting of two components: the patient and user database and the device component which allows for device setup, download and evaluation of the data. The TensioMed arteriograph uses the distance from the suprasternal notch (jugulum) to the pubic symphysis to

reflect the distance travelled by the pulse wave. The distance between these two sites is measured along the body surface with the patient in the supine position. This measurement is then inputted into the software. The TensioMed arteriograph uses a similar method as is what is used for blood pressure, in that a cuff is placed tightly around the patient's dominant arm. The hose of the cuff is then connected to the pneumatic connector on the left-hand side of the device. In the first phase a blood pressure measurement is recorded and in the second phase a pulse waveform analysis is performed. Initially the device inflates back to the measured diastolic value and registers the pulse waves for a previously determined duration (8 seconds by default). Secondly, the device inflates further to the suprasystolic value (define as the measured systolic value + 35mmHg) which occludes the brachial artery completely and registers the pulse waves for 8 seconds (by default). An arteriograph report, containing the PWV value, appears on the computer screen when the examination is complete (TensioMed) (see appendix one for an example of an arteriograph report).

Currently, the PWV threshold value used to define subclinical end-organ damage is 12 m/s as expressed in the 2007 guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) (Mancia et al., 2013).

An advantage of the PWV measurement is that it provides an extensive, non-invasive, accurate and reproducible assessment of central arterial stiffness (Mancia et al., 2013). However, the implementation of a PWV assessment into clinical practice is impeded by the lack of a standardised methodology and lack of reference values based on a large population (The Reference Values for Arterial Stiffness, 2010). It has been shown that differences in absolute PWV values exist between methodologies and populations (Millasseau et al., 2005, Weber et al., 2009). Additionally, various factors have been shown to influence PWV including age and BMI (Huybrechts et al., 2011). For example, the aorta becomes more tortuous as

people get older; therefore, age should be taken into account (Sugawara et al., 2008). Another issue with the PWV assessment is the measurement of the distance travelled by the pulse wave between the two anatomical sites. The reliability and accuracy of this measurement may be hindered if for example, the patient is a lady with a large bust size or if the patient is obese (Weber et al., 2009, Laurent et al., 2006, Huybrechts et al., 2011). Currently, there is no standardised method available to overcome these confounders.

1.7 Lifestyle factors

1.7.1 Overview of this section

There is a growing body of evidence highlighting the importance of unhealthy behaviours and their relationship with both the onset and exacerbation of psoriasis. Such behaviours include smoking (Fortes et al., 2005), excessive alcohol intake (Poikolainen et al., 1999, Kirby et al., 2008), low levels of physical activity (Frankel et al., 2012), obesity (Setty et al., 2007, Tobin et al., 2014) and drugs (Fry and Baker, 2007).

This section will provide an overview of various lifestyle factors and their association with psoriasis. The focus of this section will be on physical activity including: effects on cardiovascular health, predictors of physical activity and measures of activity.

1.7.2 Smoking

Several previous studies have postulated relationships between smoking and psoriasis. The most prominent link has been established between smoking and palmoplantar pustulosis. It has been reported that this type of psoriasis is exacerbated by smoking and perhaps even induced (Freiman et al., 2004). A study by Wolk et al (2009) also found that smokers had a 70% higher (statistically significant) risk of developing plaque psoriasis compared with non-smokers (Wolk et al., 2009). In addition, a questionnaire based twin study on smoking habits and psoriasis showed that age and childhood exposure to environmental tobacco smoke were significantly associated with psoriasis in the whole population (Lonnberg et al., 2016). It was also observed that the risk for psoriasis increased considerably for smokers with a history of >5 pack-years (even after adjusting for age, sex and childhood exposure to environmental tobacco smoke) (Lonnberg et al., 2016).

It has also been observed that smoking impacts on treatment response in patients with psoriasis. A recent retrospective study reported that smoking, together with increased body mass index and a high baseline PASI, was a risk factor for a lack of response to anti-TNF treatment (Di Lernia et al., 2014).

Other studies have looked at smoking in relation to the severity of disease, for example a study by Fortes et al (2005) investigated the smoking history of psoriasis patients in relation to the severity of their disease. This study found that the intensity (number of cigarettes smoked each day) of a patient's smoking was related to the severity of psoriasis (Fortes et al., 2005). Patients who smoked more than 20 cigarettes each day were likely to have a more severe case of psoriasis than those patients who smoked less than or equal to 10 cigarettes per day (Fortes et al., 2005). An advantage of this study is that confounding variables such as alcohol

consumption, age, sex and stress were controlled. However, it is important to note that a lot of studies attempting to clarify the relationship between lifestyle factors and psoriasis are likely to have been confounded by other variables as they are difficult to control (Freiman et al., 2004).

Various immunological mechanisms by which smoking could influence the development of psoriasis have been proposed (Fortes et al., 2005). Firstly, it has been suggested that smoking can stimulate an excessive production of interleukin-1 (IL-1, a cytokine with a role in the regulation of immune and inflammatory responses) as well as enhancing the production of tumour necrosis factor alpha (TNF-α, also a cytokine). These effects of smoking have been associated with the activation of psoriasis (Fortes et al., 2005). Secondly, smoking has been proposed to exacerbate psoriasis through oxidative tissue damage. Psoriasis patients have been shown to have low levels of anti-oxidants and therefore smoking may enhance pre-existing oxidative damage (Higgins, 2000). Further work is required to elucidate the association between smoking and psoriasis.

1.7.3 Alcohol

There has been much debate as to whether alcohol is a trigger of the disease or a consequence (Higgins, 2000). It has been suggested that alcohol consumption could be triggered by the psychological distress experienced by a large proportion of psoriasis patients. Therefore, patients may drink alcohol as a means of coping with their disease (Kimball et al., 2010a). One study has shown that both male and female psoriasis patients consume a larger amount of alcohol relative to a control group. In addition, the alcohol consumption of both male and female psoriasis patients tended to increase following the initial diagnosis of the disease (Higgins, 2000). Another study

showed that psoriasis contributed to excessive alcohol consumption in young and middle-aged men. This study compared 144 male patients with psoriasis and 285 male patients with various other skin diseases (control group). The results from this study revealed that the psoriasis patients drank, on average, twice the amount of alcohol prior to their disease onset compared to the control group (Poikolainen et al., 1990). Another study by Poikolainen et al (1999), reported an association between excess mortality and alcohol consumption in patients with moderate to severe psoriasis (Poikolainen et al., 1999). In a cohort of 3132 males and 2555 females, a total of 1918 deaths were reported, which was much higher than the deaths expected on the basis of the national mortality rates (1211). Alcohol was a major cause for this excess mortality (Poikolainen et al., 1999).

It has also been found that alcohol can exacerbate pre-existing psoriasis and cause psoriatic flare-ups. The exact mechanism by which alcohol exacerbates the disease however is unclear (Smith and Fenske, 2000). Studies have shown that alcohol consumption is independently associated with severe forms of psoriasis (Gerdes et al., 2010). Additionally, it has been observed that alcohol abusers are more resistant to therapy and have a distinct clinical disease presentation. It has been reported that patients tend to have more inflamed psoriatic lesions with an acral distribution (Smith and Fenske, 2000). Abstaining from alcohol has also been shown to improve psoriasis (Hayes and Koo, 2010).

1.7.4 Obesity

Being overweight (body mass index (BMI) greater than 25) or obese (BMI greater than 30) (Finucane et al., 2011) is associated with both the onset and exacerbation of psoriasis. Obesity is a component of the metabolic syndrome, which is a constellation of metabolic disturbances, all of which are known risk factors for CVD

(Eckel et al., 2005). These metabolic malfunctions include: glucose intolerance (e.g. Type 2 diabetes), insulin resistance, hypertension, dyslipidemia and central obesity. Collectively, these conditions are associated with an increased risk of cardiovascular disease (CVD) (Eckel et al., 2005). It has been established that these CVD risk factors are highly prevalent in patients with psoriasis (Tobin et al., 2010).

A reduction in psoriasis severity (as assessed by PASI) has been previously associated with weight loss (Naldi et al., 2014). A randomised control trial by Naldi et al (2014) assigned 303 overweight or obese patients with chronic plaque psoriasis to receive either a 20-week dietary plan with physical exercise, or simple informative counselling about weight loss for the clinical control of psoriatic disease (Naldi et al., 2014). A mean PASI reduction of 48% was observed in the dietary intervention arm, compared with a 25.5% reduction in the information only arm ($p=0.002$). It was speculated that these results were related to weight loss (Naldi et al., 2014).

A study by Tobin et al (2014) reported a significant correlation between PASI and BMI. Obese patients had significantly more severe psoriasis than patients who were not obese when compared using both BMI and waist circumference (Tobin et al., 2014). Confounding factors including, alcohol, smoking and stress were controlled for. Visceral fat is the primary source of inflammatory mediators in obesity, including adipokines such as leptin and resistin and cytokines such as IL-6 and TNF- α. The production of these mediators may lead to the exacerbation of psoriasis (Tobin et al., 2014).

It has also been reported that certain dietary components may be an important factor in relation to the severity of disease psoriasis. It has been proposed that low-calorie diets may be important in the prevention of moderate non-pustular psoriasis (Rucevic

et al., 2003). Another study concluded that obese patients with moderate to severe psoriasis can enhance their response to low-dose systemic treatment if they incorporate a calorie-controlled diet into their treatment regimen (Gisondi et al., 2008a).

Despite the evidence provided by Herron et al supporting the idea that obesity is a consequence of psoriasis, other studies have shown that obesity is a potential risk factor for the disease, predominantly in those who gain weight after 18 years (Laws et al., unpublished). For example, Hamminga et al concluded that obesity can enhance the risk of an individual developing psoriasis and it can also exacerbate the pre-existing disease. Additionally, Hamminga et al recognised that weight loss in obese psoriasis patients can improve the clinical appearance of the disease (Hamminga et al., 2006).

Obesity may induce the psoriatic phenotype through systemic inflammation in genetically susceptible individuals (Boehncke et al., 2011b). It has been observed in both psoriasis and obesity that there is an increase in the levels of T-helper 1 cytokines and adhesion molecules circulating around the body; examples of these molecules include E-selectin and intercellular adhesion molecule (ICAM)-1. The inflammatory mediators which are characteristic of both psoriasis and obesity are involved in the regulation of different processes, some of which include lipid metabolism, epidermal proliferation and angiogenesis. For example, leptin, which may increase the chance of an individual developing psoriasis or exacerbate pre-existing disease (Azfar and Gelfand, 2008).

Additionally, levels of TNF-α in the blood and skin of patient with psoriasis are increased as it is essential for the recruitment of T cells to the skin. Activated T cells promote the hyperproliferation of cells in the epidermis of the skin which is a key

feature of psoriatic plaque formation. TNF-α also has a key role in the inflammatory component of obesity and is said to be secreted by macrophages in the adipose tissue (Azfar and Gelfand, 2008, Hamminga et al., 2006).

Furthermore, adipokines, produced by the adipose tissue, influence body weight homeostasis and insulin resistance as well as alterations in lipids, blood pressure and inflammation (Van Gaal et al., 2006). Therefore, it has been hypothesised that the dysregulation of adiponectin and other hormones, including resistin may contribute to chronic inflammation (a component of psoriasis and CVD), the development of the metabolic syndrome and CVD (Laws et al., unpublished). Recent studies have shown that exercise reduces the inflammation associated with obesity. It has also been demonstrated that weight loss in obese individuals can improve vascular function as well as reducing the expression of vascular adhesion molecules (like sE-selectin) and proinflammatory cytokines. It has been hypothesised that avoidance of physical activity in patients with psoriasis may be related to the prevalence of obesity and CVD (Laws et al., unpublished). However, it is unknown as to whether physical activity simply dampens the inflammatory process, thereby reducing the risk of CVD or whether it is the modification of the CVD risk factors which lowers the CVD risk.

1.8 Physical Activity

1.8.1 Overview

Physical activity is well-known as a vital element of the prevention and management of various conditions including CVD, Type 2 diabetes mellitus, obesity and metabolic syndrome. More recently, exercise has been recommended as a key component of psoriasis management (Treloar, 2010). The World Health Organisation (WHO) defines physical activity as any bodily movement produced by skeletal muscles which

requires energy expenditure. Physical inactivity has been recognised as the fourth leading risk factor for global mortality and accounts for 6% of deaths globally, according to the WHO. Regular moderate intensity physical activity in adults, such as walking or cycling, has various significant health benefits. Many studies have shown that regular physical activity can help to reduce a person's risk of myocardial infarction and other cardiovascular events such as a stroke (Myers, 2003). Physical activity has a favourable impact on the traditional risk factors associated with CVD, for example it promotes a healthy BMI, it can help to reduce blood pressure and it can help to reduce cholesterol by lowering the levels of LDL's in the blood. People who are physically active on a regular basis may also experience some psychological benefits such as improvement in self-confidence, lower levels of stress and reduced anxiety levels (Myers, 2003). Additionally, physical activity can help to lower a person's risk of depression or reduce the symptoms on people with pre-existing depression. A sedentary lifestyle is a key risk factor implicated in CVD. A lack of physical activity can lead to individuals becoming obese thereby increasing their risk of developing CVD (Myers, 2003).

1.8.2 Physical activity and the cardiovascular system

It has been well-established that chronic, aerobic activity regimes help to improve cardiovascular function (Golbidi and Laher, 2012). Physical activity has been shown to be effective in different populations including healthy individuals who do not have any underlying risk factors (Golbidi and Laher, 2012), in older people (aged 60 and above) (Benjamin et al., 2004) and also in those individuals with cardiovascular risk factors (Hambrecht et al., 1998). Physical activity is a key component in the prevention of CVD. Prevention can be split into three categories: primary, secondary and tertiary. Primary prevention focuses on preventing the actual incidence of a

specific illness or disease and is therefore concerned with activities which promote health. Secondary prevention (also known as health maintenance) promotes early screening or detection of disease as well as measures to limit disability. Tertiary prevention is targeted at people who have developed a disease or illness and so the focus is on recovery or rehabilitation (Golbidi and Laher, 2012). Physical activity has an important role at each level of prevention. However, although there is good evidence to illustrate that physical activity can lower the risk of a person developing CVD, there is still a great deal of uncertainty regarding the underlying mechanisms (Golbidi and Laher, 2012).

1.8.3 The effects of physical activity on the heart

It has been established that physical activity can increase the levels of antioxidants in the body. Free radicals, a subgroup of reactive oxygen species (ROS), are a by-product of aerobic metabolism and are well-known for being able to exert both beneficial and deleterious effects on living systems (Golbidi and Laher, 2012). High concentrations of free radicals can cause harm to living organisms by reacting with molecules such as proteins, carbohydrates, lipids and nucleic acids. The phenomenon of hormesis has been used to describe the effects of physical activity on free radicals. This means that by being physically inactive or by taking part in excessive amounts of physical activity it can be harmful and it is moderate amounts of activity which are most beneficial (Radak et al., 2005). Regular physical activity has a positive effect in that it slows down the accumulation ROS-mediated cell damage by enhancing the levels of antioxidants in the myocardium (Golbidi and Laher, 2012).

Additionally, it has been established that physical activity increases the levels of cardiac heat shock proteins (HSP's). The heat shock response is a common cellular reaction to external stimuli such as oxidative stress, acidosis and energy depletion. The link between physical activity and the expression of HSP's in the myocardium is unclear however, a number of stresses associated with exercise such as heat stress and depletion of glucose can help to increase the levels of HSP's in cardiac muscle (Golbidi and Laher, 2012). The increased expression of HSP70 in cardiomyocytes is associated with protection against ischemic damage as well as increased cell survival (Martin et al., 1997).

Regular physical activity can also result in cardiac mitochondrial adaptations which subsequently causes a decrease in the production of ROS. This means that the

mitochondria have an increased ability to tolerate high calcium levels. It has been proposed that the decrease in the production of ROS could be linked to a decrease in superoxide production or an increase in mitochondrial antioxidant enzyme activity (Golbidi and Laher, 2012). It has been shown that the mitochondria of exercised animals can endure higher levels of calcium. Also, the mitochondria, isolated from the hearts of exercised animals, have a reduced sensitivity to calcium-induced mitochondrial permeability transition pore (mPTP) opening (Marcil et al., 2006). Additionally, exercise training induces a cardiac mitochondrial phenotype which resists apoptotic stimuli. This phenotype involves a variety of changes including an increase in the expression of endogenous antioxidant enzymes in both subsarcolemmal and intermyofibrillar mitochondria (Kavazis et al., 2008). Some other changes include a decrease in ROS- induced cytochrome c release and an increase in the expression of antiapoptotic proteins. These findings show that physical activity promotes biochemical changes in cardiac subsarcolemmal and intermyofibrillar mitochondria which results in a phenotype that is resistant to apoptotic stimuli. This supports the idea that mitochondrial adaptations as a result of physical activity contribute to activity-induced cardioprotection (Kavazis et al., 2008).

1.8.4 The effects of physical activity on the vascular system

Physical activity can have various beneficial effects on the vascular system. Firstly, it increases vascular expression of endothelial nitrous oxide synthase (eNOS) in both animals and humans. The eNOS enzyme produces nitric oxide (a key component of endothelial function) in response to a variety of stimuli (Fleming and Busse, 2003). Nitric oxide is essential for the maintenance of vascular haemostasis as it has anti-inflammatory and vasodilatory roles as well as a platelet inhibitory effect (Vita, 2002). A decrease in the bioavailability of endothelium-derived nitric oxide has been shown

to be predictive of deleterious cardiovascular events in the presence of risk factors but without signs of coronary artery disease (Schindler et al., 2003) or coronary atherosclerosis (Suwaidi et al., 2000). Physical activity causes an increase in heart rate which subsequently increases cardiac output and vascular shear stress. This then leads to an increased expression of eNOS. Physical activity also causes an increase in shear stress which stimulates the vascular production of ROS by an endothelium dependent pathway. Consequently, this results in the upregulation of eNOS (Golbidi and Laher, 2012).

Previous work has also shown that irradiation with UVA, corresponding to natural sunlight exposure, vasodilates the arterial vasculature independent of the effects of NOS and reduces blood pressure (Liu et al., 2014). The skin contains large stores of nitrogen oxides, particularly nitrate. Upon exposure to UVA irradiation, levels of circulating nitrite increase. It has been proposed that the nitrate to nitrite conversion is involved in the light-induced reduction in blood pressure. These findings have significant public health implications, with high latitude countries potentially being at a higher risk of developing cardiovascular diseases (Liu et al., 2014). Additionally, patients with psoriasis who lead a sedentary, indoor lifestyle could be at greater risk of developing CVD.

Furthermore, physical activity influences the structure of blood vessels which causes functional alterations and as a result improves blood flow. For example, it induces arteriogenesis which is the enlargement of existing blood vessels. Physical exercise training increases the diameter of various blood vessels including large arterioles, small arteries and conduit arteries (Golbidi and Laher, 2012). Various animal studies and clinical observations have reported a significant correlation between an increased coronary artery lumen and regular physical activity (Haskell et al., 1993). Physical activity also induces angiogenesis which is the formation of new

blood vessels at the level of the capillaries and resistance arterioles (Golbidi and Laher, 2012). There has been some speculation as to whether endurance training promotes angiogenesis either by a division of pre-existing endothelial cells or by bone marrow-derived endothelial progenitor and macrophage or monocyte derived angiogenic cells (Rehman et al., 2004). Some studies have suggested that physical activity can improve the mobilisation of endothelial progenitor cells in both healthy subjects and in individuals who are at risk of coronary or cardiovascular events (Richter et al., 2005). Therefore, a disruption in the regulation of angiogenesis is frequently associated with diseases which are dependent upon this process, such as atherosclerosis (Golbidi and Laher, 2012). In atherosclerosis, the process of angiogenesis can have both advantageous and adverse effects. An increase in angiogenesis can be beneficial in the healing of ischemic tissues. However, increasing angiogenesis in a primary atherosclerotic lesion could result in enlargement of the plaque. Some studies have shown that physical activity can prevent ischemia in skeletal muscles by inducing an angiogenic phenotype which is characterised by an overproduction of vascular endothelial growth factor (VEGF-a signal protein which stimulates angiogenesis) (Golbidi and Laher, 2012). Physical exercise can also exert favourable effects against atherosclerosis by enhancing the levels of endostatin (an endogenous inhibitor of angiogenesis). Subsequently, this results in the inhibition of the development of the atherosclerotic plaque by inhibiting angiogenesis in the plaque tissue (Gu et al., 2004). Further work is required to clarify these mechanisms.

Physical exercise also has an anti-inflammatory effect in vascular tissue. Inflammation has a key role in the pathogenesis of many cardiovascular diseases, including atherosclerosis. The release of proinflammatory cytokines in arterial plaques can cause tissue damage (Golbidi and Laher, 2012). It is now thought that markers of inflammation such as high sensitivity C-reactive protein (hs-CRP) may be

used to provide further insight into the status of atherosclerotic plaques. CRP is considered to be a predictor of cardiovascular risk however, it has also been shown to directly trigger vascular dysfunction (Sprague and Khalil, 2009). Physical exercise initially produces a short-term proinflammatory response which is subsequently followed by a long-term anti-inflammatory effect (Kasapis and Thompson, 2005). Regular physical activity reduces CRP and other proinflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) whilst increasing the levels of anti-inflammatory cytokines such as IL-4 (Plaisance and Grandjean, 2006).

1.8.5 Guidelines for physical activity

According to the most recent update by the Committee on Exercise and Cardiac Rehabilitation of the American Heart Association, in order to promote and maintain cardiorespiratory health, all healthy adults aged between 18 and 65 should take part in moderate-intensity aerobic physical activity for a minimum of 30 minutes on 5 days on 3 days each week (Haskell et al., 2007). Similarly, the most recent UK guidelines for physical activity recommend that adults should undertake a minimum 150 minutes of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity per week, in bouts of 10 minutes or more (Craig and Mindell, 2013).

Alternatively, a combination of moderate and vigorous physical activity to achieve a total energy expenditure of ≥500-1000 MET-minutes/week can be performed (Garber et al., 2011). Volume of activity can be computed by weighting the type of activity by its energy requirements defined in metabolic equivalent (MET) values to yield a score in MET-minutes. MET's are multiples of the resting metabolic rate and a MET-minute is computed by multiplying the MET score of an activity by the minutes performed. Vigorous-intensity activity (defined as >6.0 metabolic equivalents or METs) performed

for a particular duration and frequency results in greater energy expenditure than moderate-intensity activity (defined as 3-6 METs) of the same duration and frequency (Haskell et al., 2007). Although the guidelines for adults over the age of 65 are the same, however, it is advised that moderate and vigorous-intensity activities are performed relative to an individual's ability (Nelson et al., 2007). For example, on a ten-point scale where sitting is 0 and maximum effort is 10, moderate-intensity activity is around a 5 or a 6 and there is a noticeable increase in heart rate and breathing. On the same scale, vigorous-intensity activity is a 7 or greater and produces a large increase in heart rate and breathing (Nelson et al., 2007). Additionally, the most recent UK guidelines recommend that older adults should incorporate physical activity to improve balance and coordination on at least 2 days a week (Craig and Mindell, 2013).

1.8.6 High-intensity interval training

High-intensity interval training (HIIT) is a form of physical activity which involves alternating between high-intensity anaerobic periods of activity and lower-intensity activities or resting periods. HIIT is designed to be performed with maximum effort to be as beneficial as possible. It is now thought that this type of training is more effective than moderate-intensity continuous training (MICT) (Sijie et al., 2012). Previous studies have shown that HIIT is more effective in improving brachial artery vascular function, perhaps due to the positive effects this type of training has on cardiorespiratory fitness, traditional CVD risk factors, oxidative stress and body fat (Ramos et al., 2015).

An example of a HIIT programme is the '4 x 4' protocol which consists of four intervals for four minutes at 85-95% of the maximum heart rate with active recovery periods at

50-70% of the maximum heart rate (Ramos et al., 2015). Studies have shown that individuals who followed the 4 x 4 HIIT protocol for 12-16 weeks (three times per week) had significantly enhanced vascular-dependent function in comparison to individuals who followed a MICT programme (Wisløff et al., 2007, Tjønna et al., 2008). MICT programmes are characterised by activity which requires 70% of the maximum heart rate. Previous work has also shown improvements in cardiorespiratory fitness as measured by either maximal oxygen uptake or peak oxygen uptake, following 12 weeks of HIIT, three times per week compared with MICT. A study by Mitranun et al (2014), with Type 2 diabetic adults, found that individuals on the HIIT programme had greater improvements in their aerobic fitness as well as improvements in lipid profiles and glycemic control (Mitranun et al., 2014).

Additionally, a study by Wisloff et al (2007) observed that HIIT induced a significant enhancement in antioxidant status when compared with MICT in patients with heart failure (Wisløff et al., 2007). Similarly, the study by Mitranun et al (2014) reported an increase in glutathione peroxidase (an enzyme which provides protection against oxidative damage) following HIIT (Mitranun et al., 2014). Studies have also shown a significantly greater increase in nitrous oxide bioavailability as a result of HITT when compared to MICT (Wisløff et al., 2007, Tjønna et al., 2008).

It has been postulated that the ability of HIIT to improve vascular function may be due to the increased blood flow through the vessels supplying oxygen to the working muscles, which subsequently promotes greater shear stress-induced nitrous oxide bioavailability (Wisløff et al., 2007, Tjønna et al., 2008, Ramos et al., 2015). This is supported by previous work by Thijssen et al (2009) who found that blood flow and shear stress increased with increasing intensity of activity (Thijssen et al., 2009). In concordance with this theory, studies have also shown that chronic low shear stress in sedentary individuals, as a result of inactivity, may increase levels of biomarkers

associated with vascular dysfunction, for example pro-inflammatory markers (Vion et al., 2013) and cell-adhesion molecules (Wang and Liao, 2004).

1.8.7 Activity norms within the general population

According to the most recent Health Survey for England (2012) 67% of men and 55% of women, aged 16 and over, met the guidelines for aerobic activity of at least 150 minutes or moderate-intensity activity or 75 minutes of vigorous-intensity activity or an equivalent combination of the two. It is important to note that generally, fewer women are meeting these guidelines than men. In both sexes, the proportion who met the guidelines generally decreased as age increased. It was reported that, 16-24-year-old males were most likely to adhere to the guidelines whereas in women the proportion meeting the guidelines rose to a peak among those aged 35-44 before decreasing as age increased. There was a significant decline in the proportion adhering to the guidelines in individuals aged 74 and above among both sexes (Craig and Mindell, 2013).

1.8.8 Predictors of physical activity

The findings from Health Survey England revealed various demographic predictors of physical activity including age, sex, location, household income and BMI (Craig and Mindell, 2013). Levels of physical activity appear to be consistently higher in men. Previous studies have also reported higher levels of physical activity in males (Azevedo et al., 2007, Troiano et al., 2008). It has been proposed that the reason for this is because men enjoy taking part in physical activity whereas women engage in physical activity with the goal of either improving their health or their physical appearance therefore they see it as more of a chore (Azevedo et al., 2007). The WHO has suggested that women have limited time available to engage in physical activity as they may have a workload in the home and/or care-giving roles within the family. Research has shown that parenthood affects women's participation in physical activity in that women with children tend to engage in activity less than those without children (Verhoef et al., 1993). Cultural expectations of women may also restrict their participation in some physical activities.

Generally, it was also found that physical inactivity increases with age. This age-related decline in physical activity is thought to have a biological basis (Ingram, 2000). Decreasing levels of physical activity with age appear to be associated with altered neurotransmission involving the central dopamine system (Sallis, 2000). It is believed that a reduction in dopamine release or loss of dopamine receptors underpin age-related activity reduction (Ingram, 2000). However, there are various other barriers to exercise engagement in adults aged 65 and over. One of the most common reasons given by older adults for not taking part in physical activity is ill-health, pain and injury (Schutzer and Graves, 2004). Additionally, elderly individuals deem physical activity as time consuming and tend to see it as a recreational pursuit as opposed to a way

of improving overall health and wellbeing (Chao et al., 2000). Healthcare practitioners often advise older adults to try and be more physically active. However, this advice is often very general and rather vague. Recent work, in patients with psoriasis, has shown that clinicians recognise the importance of lifestyle behaviours in these patients; however, they do not believe it is their role to facilitate lifestyle behaviour change (Nelson et al., 2014). In order to encourage lifestyle behaviour change, it could be that the advice provided by healthcare practitioners needs to be more specific. For example, in the context of physical activity, advice on the type and quantity of physical activity may be more effective.

The physical environment in which people live in has been shown to influence engagement in physical activity (Schutzer and Graves, 2004). It has been reported that access to parks and other recreational facilities, safe footpaths and areas which are relatively free from crime were all important factors in people's decisions to take part in physical activity (Schutzer and Graves, 2004, Taylor, 2014). It has been observed that older adults, whose preferred choice of activity was walking, demonstrated higher levels of physical activity when they perceived higher safety levels within their neighbourhoods (Schutzer and Graves, 2004).

It was also observed from the Health Survey England that the proportion of individuals adhering to the guidelines for aerobic activity increased as household income increased. This pattern was the same for both sexes; 76% of men and 63% of women in the highest quintile of equivalised household income met the guidelines for physical activity. In contrast, only 55% of men and 47% of women in the lowest income quintile adhered to the guidelines. Previous research has proposed various explanations for this trend. It has been suggested that inferior education may not provide training in a variety of physical activity skills thereby reducing the range of opportunities to participate in physical activity (Lee and Ho, 2012). Additionally, lower household

income may prevent people from being able to afford equipment, shoes, garments, or memberships necessary for certain types of physical activity (Lee and Ho, 2012). People from lower socioeconomic backgrounds also tend to work longer hours or multiple jobs which may mean that time to participate in physical activity is limited (Lee and Ho, 2012).

The Health Survey England also reported a link between BMI and exercise engagement (Craig and Mindell, 2013). It was found that both men and women who were overweight (BMI over 25) or obese (BMI over 30) were less likely to have adhered to the guidelines for moderate and vigorous-intensity physical activity than those who were not overweight or obese. It was documented that 75% of men who were not overweight or obese met the guidelines in comparison with 71% of men who were overweight and 59% of men who were obese. Similarly, 64% of women who were not overweight or obese met the guidelines, compared with 58% of overweight and 48% of obese women, respectively (Craig and Mindell, 2013).

1.8.9 Physical activity and psoriasis

The role of physical activity in the prevention or attenuation of psoriasis remains uncertain (Frankel et al., 2012). A recent study by Frankel et al (2012) prospectively evaluated the association between physical activity and incident psoriasis in a large United States cohort of women. This study incorporated an assessment of the association between the type of physical activity and the risk of psoriasis (Frankel et al., 2012). Interestingly, this study found that vigorous physical activity was independently associated with a reduced risk of developing psoriasis. This association was also shown to remain significant following the adjustment for BMI. The results from this study suggest that by taking part in at least 20.9 MET-hours per

week of vigorous exercise (which is equivalent to 105 minutes of running or 180 minutes of swimming or playing tennis), a person can reduce their risk of psoriasis by 25-30% (Frankel et al., 2012). Furthermore, this study concluded that an increase in participation in vigorous physical activity would help to decrease the incidence of various comorbidities associated with psoriasis, including coronary heart disease, myocardial infarction and stroke (Frankel et al., 2012).

In terms of how physical activity decreases the risk of developing psoriasis, this is an area which requires further research. It has been proposed that vigorous physical activity could dampen a state of chronic inflammation and/or immune activation which predisposes a person to developing psoriasis. An overexpression of proinflammatory cytokines is a key feature of psoriasis pathogenesis and therefore conditions which are characterised by increased chronic inflammation, such as obesity, may put people at an increased risk for developing psoriasis (Setty et al., 2007). Physical activity is known to reduce the levels of proinflammatory cytokines for example, tumour necrosis factor, IL-6 and leptin (Kondo et al., 2006). Additionally, physical activity can increase the levels of anti- inflammatory cytokines such as adiponectin, independent of BMI (Frankel et al., 2012). A study by Mora et al found that among women with similar BMI's, those who were more physically active appeared to have lower levels of the inflammatory marker CRP (Mora et al., 2006). This suggests that physical activity could potentially improve pre-existing psoriasis.

It has also been proposed that the beneficial effects of physical activity could perhaps be mediated by its effect on mood (Frankel et al., 2012). Regular exercise has been shown to improve a person's emotional well-being and decrease levels of stress and anxiety. In addition, it has been shown that exercise can be an effective treatment for depression (Mead et al., 2008). Evidence has shown that stressful life events are associated with new-onset psoriasis and can exacerbate pre-existing disease. It is

thought that psychological stress has an impact on psoriasis via increased T cell activation (Naldi and Gambini, 2007).

1.8.10 Patterns of physical activity in patients with psoriasis

Currently, the literature on patterns of physical activity in patients with psoriasis is limited. It has previously been observed by Torres et al (2014) that 18.9% (n=90) of people with psoriasis fail to meet the guidelines for physical activity (Torres et al., 2014). In some studies, this type of observation has correlated with psoriasis severity, as measured by the PASI (Al-Mazeedi et al., 2006). Patients with psoriasis (with a psoriasis area severity index (PASI) score ≥10) feared the reactions of others when participating in sports and consequently they avoided fitness centres and public swimming pools (Khoury et al., 2014). However, the psoriasis-specific barriers to exercise engagement and the types of exercise undertaken by individuals with psoriasis remain unexplored.

1.8.11 Measures of physical activity

Levels of physical activity are often monitored in order to evaluate the health behaviours of the population and their association with health status, including mortality and morbidity rates. In terms of research, measures of physical activity are also important when assessing the effectiveness of interventions (Prince et al., 2008). There are various methods available for monitoring levels of physical activity, some of which include: self-report measures (questionnaires, diaries, surveys and interviews) and objective or direct measures (calorimetry, physiologic m a r k e r s , accelerometers, pedometers and heart rate monitors). Despite the advantages of using direct methods to assess levels of physical activity, they are often time and cost

intensive. Some of these measures also require specialist training. There is no 'gold standard' measure for assessing physical activity (Prince et al., 2008).

1.9 The International Physical Activity Questionnaire

The International Physical Activity Questionnaire (IPAQ) is a tool which was developed in order to standardise assessment of physical activity in different countries. The IPAQ is a 7-item questionnaire which identifies the type and the quantity of physical activity that individuals do as part of their everyday lives in (Craig et al., 2003). There are two forms of the IPAQ: a short-version and a long version. The long form of the IPAQ assesses physical activity undertaken across a comprehensive set of domains including: leisure time physical activity, domestic and gardening activities, work-related physical activities and transport-related physical activity. The short form of the IPAQ (IPAQ-S) assesses specific types of activity undertaken across the four domains, including: walking, moderate intensity activities and vigorous-intensity activities (defined as exercise needing hard physical effort for at least 10 minutes per session). The items on the short form of the IPAQ are structured to provide individual scores for walking, moderate-intensity and vigorous-intensity activity. Individuals are asked to record how many days, in the previous week, they engaged in waking, moderate-intensity and vigorous-intensity activity. Additionally, they are asked to document how long they spent engaging in each type of activity. The final item on the IPAQ is the 'sitting question' which asks how long a patient spends sitting on a daily basis. This item is an additional indicator variable of sedentary behaviour and is not included as part of the overall IPAQ score. Computation of the total IPAQ score involves summation of the duration (in minutes) and frequency (in days) of each type of activity, generating both a categorical score (1, 2 or 3) and a continuous score (MET-minutes/week). See section 3.5.2 for more details on scoring of the IPAQ.

The IPAQ was first published with its validation based on a 12-country sample. The authors recommended the use of the short-form IPAQ for the national monitoring of physical activity and the long-form for research requiring a more detailed assessment of physical activity (Craig et al., 2003). An advantage of using a questionnaire, like the IPAQ, to assess levels of physical activity is that it is practical, cost-effective and the burden it has on participants is low (Prince et al., 2008). On the other hand, the IPAQ has been criticised for overestimating levels of physical activity. Reasons for the overestimation of physical activity may include social desirability and inaccurate memory (Rzewnicki et al., 2003, Prince et al., 2008). The tendency to provide socially desirable responses varies across social groups which may have different norms and values regarding the desirability of the behaviour being assessed (Rzewnicki et al., 2003). Another drawback of the IPAQ is that it may not reliably reflect an individual's cardiovascular fitness and therefore may not predict health outcomes as clearly as an objective measure of cardiovascular fitness, such as an accelerometer (Hein et al., 1992, Taylor, 2014).

1.10 Diastolic Reflection Area

The DRA is a dimensionless index which provides information about the quality of diastolic filling condition of the left coronary artery during diastole. The higher the DRA value, the better the filling condition of the left coronary artery during diastole. The DRA is also thought to provide information about cardiac fitness. Very little data have been published on the DRA.

1.11 Conclusions and Gaps Identified in the Literature

From the dermatological perspective, a treatment aimed at reducing the severity of psoriasis should also help to reduce the inflammatory burden of the disease. However, it is also very important to monitor known modifiable cardiovascular risk factors, such as obesity and smoking, which tend to be common amongst individuals with psoriasis. Poor control of such unhealthy behaviours could result in sustained chronic inflammation and a higher risk of developing atherosclerosis and other cardiovascular-related comorbidities (González-Gay et al., 2012). This should be taken into consideration by the dermatologist and they should perhaps incorporate a primary cardiovascular risk prevention strategy into the patient's treatment plan. For example, in terms of physical activity, the clinician could discuss with the patient how they might incorporate physical activity into their lifestyle, along with the type of activities which would be beneficial for them personally and the duration of activity that would be appropriate for that person on a daily/weekly basis. Unfortunately, there are no guidelines in place at present which specifies how to deal with the management of cardiovascular risk in psoriasis patients (González-Gay et al., 2012). In the context of physical activity, this is because the relationship between physical activity, specifically the type (intensity) or duration of physical activity and cardiometabolic risk has not been assessed. Additionally, it is unknown as to what the barriers to physical activity are in this group of patients.

Furthermore, there seems to be little work into the role of exercise and the specific type of exercise in reducing the CVD risk in patients with psoriasis. The study by Frankel et al 2012 (mentioned above) incorporated an assessment of the relationship between the type of physical activity (e.g. moderate or vigorous exercise) and the risk of developing psoriasis. It was interesting to see that vigorous physical activity was independently associated with a reduced risk of developing psoriasis (Frankel et al.,

2012). This raises the possibility that exercise could be important in reducing the risk of CVD in psoriasis patients. Additionally, the level of reduction of CVD risk could be influenced by the type of physical exercise. Frankel's study observed that by taking part in at least 20.9 MET-hours per week (e.g. 105 minutes of running) of vigorous exercise, a person can reduce their risk of psoriasis by 25-30%. This study also found that an increase in participation in vigorous physical activity would help to decrease the incidence of various comorbidities associated with psoriasis, including coronary heart disease, myocardial infarction and stroke. This poses the question of whether vigorous physical exercise could reduce the CVD risk in patients with pre-existing disease.

CHAPTER TWO: AIM, HYPOTHESES AND RESEARCH QUESTIONS

2.1 Overarching research aim

The overarching research aim of this PhD is to investigate the importance of physical activity on cardiovascular disease risk in patients with psoriasis.

2.2 Hypotheses

The purpose of this PhD was to interrogate the following hypotheses:

i) Individuals with psoriasis are less likely to engage in physical activity for reasons which may be related to their psoriasis.

ii) Physical activity is important for cardiovascular health in patients with psoriasis and objective measurement of the amount of activity undertaken by patients with psoriasis has clinical utility.

iii) Blood levels of sE-selectin, metabolic biomarkers, circulatory lipids, adipokines and inflammatory biomarkers are indicative of cardiorespiratory fitness and arterial stiffness in patients with psoriasis, but can be influenced by physical activity.

2.3 Research questions

In order to interrogate the hypotheses presented in section 2.2, three fundamental research questions were posed. The experimental work addressing each question is presented in chapters four, five and six. The primary research questions were then broken down further into smaller individual questions which map onto the statistical analyses presented in the subsequent results chapters.

Research question one (study one; chapter four)

What are the barriers to cardiorespiratory fitness in patients with chronic plaque psoriasis?

Work addressing research question one is presented in study one which is in chapter four of this thesis. This work interrogated hypothesis i) *individuals with psoriasis are less likely to engage in physical activity for reasons which may be related to their psoriasis* (see section 2.2).

Study one explored whether there was a relationship between psoriasis severity, (as measured by the DLQI, PASI and SPI) and patterns of physical activity and also whether there were any psoriasis-specific barriers to physical activity which could potentially be used to inform patient management in the future.

Research question two (study two; chapter five)

Is self-report physical activity associated with arterial stiffness and cardiorespiratory fitness in patients with psoriasis?

Work addressing research question two is presented in study two which is in chapter five of this thesis. This work interrogated hypothesis ii) *physical activity is important for cardiovascular health in patients with psoriasis and objective measurement of the amount of activity undertaken by patients with psoriasis has clinical utility* (see section 2.2).

Study two assessed the relationship between pulse wave velocity (PWV: a pre-clinical marker of future cardiovascular events) and diastolic reflection area (DRA: a proposed measure of cardiorespiratory fitness). This study also evaluated the relationship between arterial stiffness (PWV) and self-reported levels of physical activity. Additionally, this study explored whether self-report physical activity was a valid measure of activity levels when compared to an objective measure of cardiorespiratory fitness (DRA) in patients with psoriasis. Finally, study two determined whether the PWV and DRA parameters provided a valid indication of self-report sedentary behaviour.

Research question three (study three; chapter six)

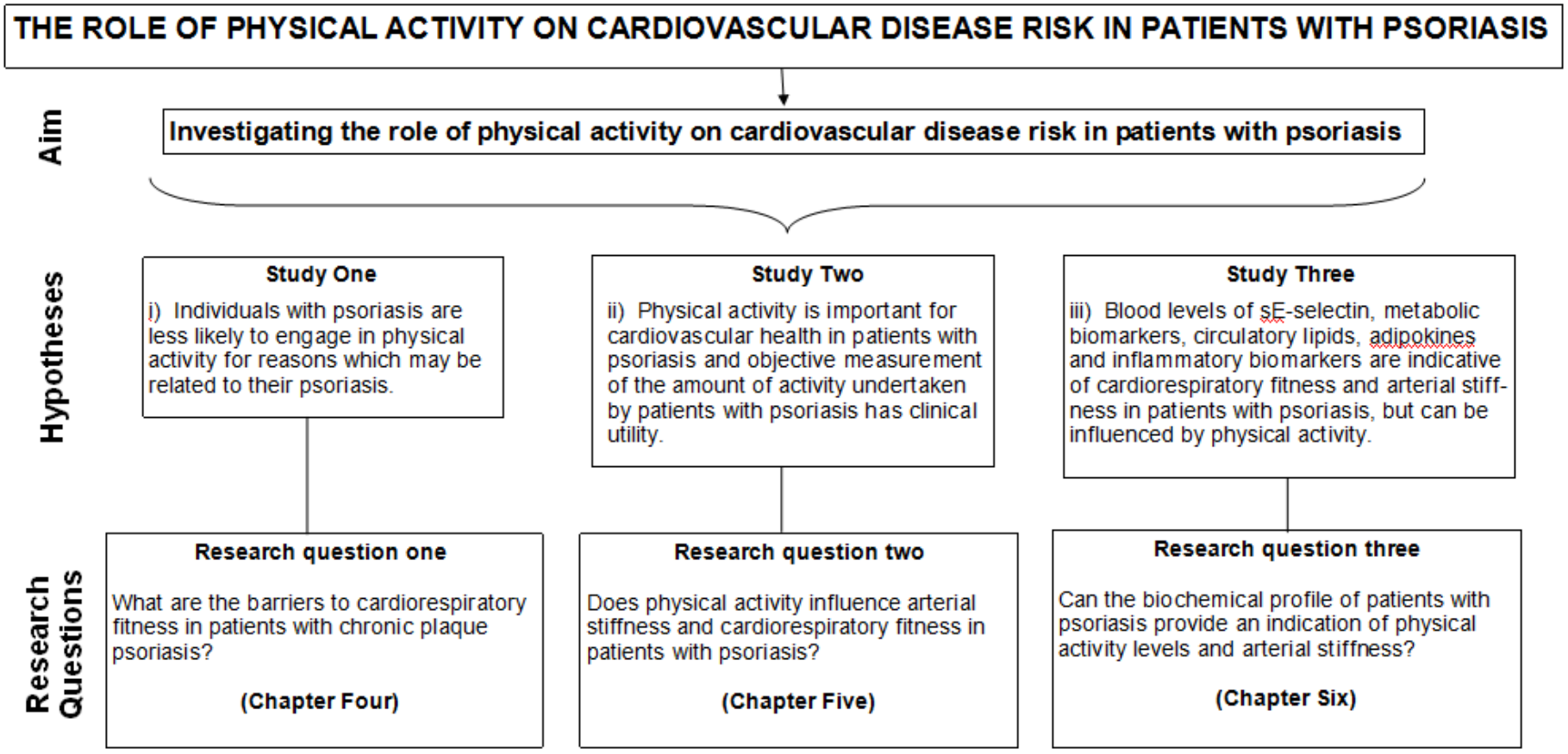
Is self-report physical activity a significant predictor of biomarker concentration, arterial stiffness (PWV) and cardiorespiratory fitness (DRA) in patients with psoriasis?

Work addressing research question three is presented in study three which is in chapter six of this thesis. This work interrogated hypothesis iii) *blood levels of sE-selectin, metabolic biomarkers, circulatory lipids, adipokines and inflammatory biomarkers are indicative of cardiorespiratory fitness and arterial stiffness in patients with psoriasis, but can be influenced by physical activity* (see section 2.2).

Study three explored the relationship between self-report physical activity and the biochemical profile (including sE-selectin, metabolic markers, adipokines, circulatory lipids and inflammatory markers) of patients with psoriasis. Additionally, the relationship between biochemical profile and, a) arterial stiffness (PWV), b) cardiorespiratory fitness (DRA) and c) physical severity of psoriasis, as measured by the PASI was also assessed in study three.

Furthermore, study three determined whether physical activity was a significant predictor of the biochemical profile of people with psoriasis, even when controlling for demographic factors and psoriasis severity measures. Finally, this study assessed whether the biochemical profile of patients with psoriasis and/or their physical activity levels were predictive of a) their arterial stiffness (PWV) and b) their DRA, even when controlling for demographic factors and psoriasis severity measures.

Figure 2.1 A schematic depicting the aim and hypotheses of this PhD along with the three primary research questions.



CHAPTER THREE: METHODS

3.1 Summary

This chapter will highlight the study design used to address the thesis objectives, including the recruitment process and assessments performed during study visits. My PhD comprises 3 main studies, therefore this chapter will detail the different methodologies used in each study along with information regarding data cleaning and validation. The analysis techniques are also summarised and towards the end of the chapter there is a conclusion which signposts the content of subsequent results chapters.

3.2 Study design

My PhD is made up of three studies, all of which are exploratory observational studies with a cross-sectional design. Each study was carried out in patients with Type 1 chronic plaque psoriasis.

3.2.1 Ethics

These studies were approved by the Salford NHS Research Ethics Committee (ethics numbers: 11/NW/0654, 12/NW/0239 and 10/H1003/10) and were conducted in accordance with the Declaration of Helsinki principles. Written, informed consent was obtained from each participant prior to data collection.

3.3 Participants

Participants within the three studies were sourced from both primary and secondary care (71% of patients were from primary care). The primary care cohort consisted of people with chronic plaque psoriasis, over the age of 18, from 13 primary care practices across the North West of England. A total of 287 patients were recruited from both deprived and affluent areas as part of a large National Institute for Health Research (NIHR) funded study (the Identification and Management of Psoriasis Associated Comorbidity [IMPACT] programme) (Nelson et al., 2015). In total, 17% (n=48) of these patients had co-existent psoriatic arthritis and 31% (n=89) were on active treatment (defined as UVB, PUVA, systemic therapies and biologics; data on topical treatments was not collected).

The secondary care cohort comprised people with chronic plaque psoriasis between the ages of 18 and 55. A total of 117 participants, from secondary care, were recruited from the Manchester Psoriasis Clinic (Salford Royal Hospital), a regional secondary and tertiary care centre serving the North West of the United Kingdom and Primary Care centres with the same geographical footprint. In total 30% (n=35) of these patients had co-existent psoriatic arthritis and 48% (n=56) were on active treatment (defined as UVB, PUVA, systemic therapies and biologics; data on topical treatments was not collected).

Recruitment

Participants responded to promotion of the studies through posters and leaflets placed in community venues across the North West of England, such as libraries and shops and informal talks to community groups. Participants from secondary care were recruited through informal discussions during their routine visits to the Manchester Psoriasis Clinic at Salford Royal Hospital. Purposive sampling (a non-probability

sampling technique, whereby the researcher focuses on certain characteristics, with respect to the inclusion criteria of the study and chooses to recruit individuals who match the criteria) and snowballing (a non-probability sampling technique whereby existing participants recruit future participants from among their acquaintances), enabled diversity in terms of participant gender, age, socio-economic background, self-identified ethnicity and self-assessed psoriasis severity, duration and treatment.

3.3.1 Exclusion criteria

Participants were excluded from the study if they did not have psoriasis, were pregnant or breastfeeding, suffered with severe mental health problems, were recently bereaved, had a terminal illness or if there were issues with capacity and consent.

3.4. Overview of study assessments

Study participants attended two visits to the clinic. This section will provide a brief overview of the assessments carried out, preceding a more detailed description in subsequent sections.

3.4.1 Participant assessment

Participants were recruited from both primary and secondary care. Each participant underwent a: medical history, lifestyle factors, blood pressure, height and weight, waist and hip circumference for waist-hip ratio and current medication. Recruited participants underwent a PASI assessment (an objective measure of psoriasis severity carried out by a practitioner; see section 3.5.2), and were asked to complete

a self-reported assessment including the International Physical Activity Questionnaire (IPAQ) and the Dermatology Life Quality Index (DLQI) and the Simplified Psoriasis Index (SPI).

A blood analysis was also carried out for each participant. This analysis involved the measurement of the following biomarkers: glycated haemoglobin (HbA1C), fasting lipids (total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides), fasting glucose, C-reactive protein (CRP) and liver and renal function. Participants recruited from secondary care had an additional sample of venous blood collected into ethylenediamine tetra-acetic acid (EDTA) tubes for further analysis (see section 3.7).

Subsequently, 60% of participants consented to an arterial function assessment. The respondents from primary care attended a clinic at their local general practice and respondents from secondary care attended an appointment at the Wellcome Trust Clinical Research Facility at the University of Manchester.

3.5 Study one: what are the barriers to cardiorespiratory fitness in patients with psoriasis?

3.5.1 Overview

404 participants were recruited from primary and secondary care to this study. This work interrogated hypothesis i) *patients with psoriasis have compromised cardiac fitness and are at an increased risk of future cardiovascular events, partly as a consequence of avoiding physical activity* (see section 2.2).

Study one explored whether there was a relationship between psoriasis severity, (as measured by the DLQI, PASI and SPI) and patterns of physical activity and also whether there were any psoriasis-specific barriers to physical activity which could potentially be used to inform patient management in the future.

This section will provide a more detailed overview of the assessments used in Study one of this PhD. A copy of each of the assessments used in this study can be found in appendix one.

3.5.2 Study one assessments

Psoriasis Area Severity Index

The PASI was used to assess psoriasis severity (Fredriksson and Pettersson, 1978). The PASI is the most widely used measurement tool for psoriasis in clinical trials. Furthermore, it is a validated measure of disease severity in chronic plaque psoriasis.

The PASI combines the assessment of the severity of lesions and the body surface area (BSA) affected into a single score in the range of 0 (no disease) to 72 (maximal disease). According to the National Institute for Health and Care Excellence (NICE) guidelines a PASI of ten or greater indicates severe psoriasis. A PASI of more than ten has been shown to correlate with a number of indicators commonly associated with severe disease, such as the need for hospital admission and systemic therapy (Finlay, 2005).

International Physical Activity Questionnaire

The short form of the IPAQ, as used in these studies, assesses specific types of activity undertaken across the four domains, including: walking, moderate intensity activities and vigorous-intensity activities (defined as exercise needing hard physical effort for at least 10 minutes per session). The items on the short form of the IPAQ are structured to provide individual scores for walking, moderate-intensity and vigorous-intensity activity. Patients were asked to record how many days, in the previous week, they engaged in waking, moderate-intensity and vigorous-intensity activity. Additionally, they were also asked to document how long they spent engaging in each type of activity. The final item on the IPAQ is a ‘sitting question’ which documents how long a patient spends sitting on a daily basis. This item is an additional indicator variable of sedentary behaviour but is not included as part of the

overall IPAQ score.

The overall IPAQ score was calculated in two different ways generating both a categorical score (1, 2 or 3) and a continuous score (MET-minutes/week). Computation of the total score or category required summation of the duration (in minutes) and frequency (in days) of each type of activity. In order for the computation of the continuous score for each individual type of activity, MET values were used. These values are different for each type of activity: walking (MET value: 3.3), moderate (MET value: 4.0) and vigorous (8.0) physical activity. The chosen MET values were derived from work undertaken as part of the IPAQ reliability study in 2000-2001 (Craig et al., 2003). These MET values were then used in a formula in order to calculate the continuous score for each type of activity. The formulas used are illustrated in figure 3.1 and table 3.1 summarises the scoring system for the short version of the IPAQ.

Figure 3.1 Formulas used for the computation of the continuous IPAQ scores.

Walking MET-minutes/week: 3.3*minutes of walking*days walking

Moderate MET-minutes/week: 4.0*minutes of moderate activity*days of moderate activity

Vigorous MET-minutes/week: 8.0*minutes of vigorous activity*days of vigorous activity

Total physical activity MET-minutes/week = sum of Walking + Moderate + Vigorous MET-minutes/week scores

Table 3.1 Scoring system for the short-version of the IPAQ.

Level of Physical Activity	Criteria
Low – Category 1	Those individuals who not meet criteria for Categories 2 (moderate) or 3 (vigorous) are considered to have a 'low' physical activity level.
Moderate – Category 2	a) 3 or more days of vigorous-intensity activity of at least 20 minutes per day OR b) 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day OR c) 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum total physical activity of at least 600 MET-minutes/week.
High – Category 3	a) vigorous-intensity activity on at least 3 days achieving a minimum total physical activity of at least 1500 MET-minutes/week OR b) 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum total physical activity of at least 3000 MET-minutes/week.

IPAQ data cleaning and truncation

The IPAQ data collected in this study was cleaned and a decision was made to truncate according to the guidelines provided by the IPAQ research committee, listed below:

- Responses to duration (time) provided in the hours and minutes' response option was converted from hours and minutes into minutes.
- If patients selected the 'don't know' or 'refused' option or data were missing for time or days the case was removed from the analysis. This is because both the number of days and daily time spent engaging in each type of activity is required for the generation of categorical and continuous summary variables.
- Only values of 10 or more minutes of activity were included in the calculation of summary scores. The rationale for this being that evidence suggests that bouts of at least 10 minutes or more are required to achieve noticeable health benefits (Haskell et al., 2007). Therefore responses to daily time spent doing a particular type of activity of less than 10 minutes were recoded as 0.
- Time variables for walking, moderate and vigorous-intensity physical activity, which exceeded 180 minutes, were recoded to be equal to 180 minutes. This truncation guideline permits a maximum of 21 hours of activity/week to be reported for each type of activity. The purpose of this was 2-fold: 1) to attempt to normalise the distribution of activity levels, which tend to be skewed in large populations and 2) to prevent misclassification of the 'high' category because although some individuals may fall into this category, their pattern of activity may not yield the health benefits in which the 'high category is intended to represent.

AHA guidelines as a 'gold standard' measure of exercise engagement

The AHA provide a set of guidelines detailing how much physical activity a healthy adult should do on a weekly basis in order to maintain their cardiorespiratory fitness (see section 1.8.5). Based on these guidelines a new variable was created in this study by adding together the individual scores for moderate and vigorous-intensity activity. Each participant was then assigned a code: 1=yes, they adhere to the AHA guidelines for physical activity or 2=no they do not adhere to the AHA guidelines for physical activity. See section 3.5.4 for how this variable was used in the statistical analysis.

Dermatology Life Quality Index

The DLQI, developed by Finlay and Khan, was used to assess the impact of the patients' psoriasis on their quality of life over the previous 7 days (Finlay and Khan, 1994). It is a self-report questionnaire consisting of 10 items. The questions cover a range of topics including: symptoms and feelings, daily activities, occupation or education, leisure, relationships and treatment. Each question has 4 alternative responses: 'not at all,' 'a little,' 'a lot,' or 'very much' with corresponding values of 0, 1, 2 and 3, respectively. Some of the items have a 'not relevant' option which is scored as 0 (see appendix one for a copy of the DLQI). The total DLQI score is calculated by summing the score of each item (Finlay and Khan, 1994). A score out of 30 is generated: 0 indicating that psoriasis has no effect on quality of life and 30 indicating that psoriasis has a significant impairment on quality of life (Gniadecki et al., 2012). According to the NICE guidelines a DLQI score greater than 10 indicates that psoriasis is having a considerable impact on a person's quality of life.

DLQI items chosen for analysis

Six items from the DLQI were chosen for the statistical analyses. As displayed in table 3.2, these items explored the following factors: skin sensitivity, embarrassment, clothing choices, social/leisure activities, engagement in sport and treatment for psoriasis. The rationale for selecting these six items was that they were the most relevant for examining psoriasis-specific barriers to physical activity.

Four items of the DLQI which were excluded from the analysis: items 3, 7, 8 and 9. These questions ask about: how a person's skin has interfered with them going shopping or looking after their home or garden (item 3), whether their skin has prevented them from working or studying (item 7), how much their skin has created problems with their partner or close friends or relatives (item 8) and how much their skin has caused any sexual difficulties (item 9). These were not deemed relevant in terms of patterns of physical activity in patients with psoriasis.

Table 3.2 Items of the DLQI chosen for statistical analysis on the basis of the responses to these items potentially impacting on a person's decision to engage in physical activity.

DLQI	Over the last week:
Item 1	How itchy, sore, painful or stinging has your skin been?
Item 2	How embarrassed or self-conscious have you been because of your skin?
Item 4	How much has your skin influenced the clothes you wear?
Item 5	How much has your skin affected any social or leisure activities?
Item 6	How much has your skin made it difficult to play sport?
Item 10	How much of a problem has the treatment of your skin been, for example by making your home messy or by taking up time?

The Simplified Psoriasis Index

The SPI is a summary measure of psoriasis which is composed of 3 individual components: current severity (SPI-s), psychosocial impact (SPI-p), disease history and interventions (SPI-i) (Chularojanamontri et al., 2013).

For this PhD the SPI-p and SPI-i were chosen for the analysis. The SPI-p score converts a 10 centimetre visual analogue rating to the nearest integer, ranging from 0-10, with 0 indicating that psoriasis has no psychosocial impact and 10 indicating that psoriasis has a significant psychosocial impact on the individual (Chularojanamontri et al., 2013). The SPI-i score consists of 10 items, 4 of which cover disease course and 6 which cover previous interventions, as shown in figure 3.2 (Chularojanamontri et al., 2013).

Figure 3.2 Part 3 of the self-assessed SPI focusing on disease history and interventions (Chularojanamontri et al., 2013).

PART 3 (SPI-i) Give 1 point for each true statement / for each therapy received (whether current or in the past).	Point
About the patient's psoriasis	
Patient has had psoriasis for more than 10 years	
Patient has had psoriasis for more than 20 years (additional point)	
Patient has had erythrodermic or generalised pustular psoriasis	
Patient has been admitted to hospital for psoriasis	
About patient's treatment	
Patient has had at least 1 course of UV treatment or PUVA	
Patient has been treated with methotrexate (now or in past)	
Patient has been treated with acitretin or etretinate (now or in past)	
Patients has been treated with ciclosporin (now or in past)	
Patients has been treated with a 'biological' drug (now or in past) Biological drugs include: Remicade/Infliximab, Enbrel/Etanercept, Raptiva/Efalizumab, Humira/Adalimumab, Stelara/Ustekinumab	
Patient has been treated with another systemic agent for psoriasis (now or in past) Name of treatment……..	
	SUM

Modification of the SPI-i variable

For the purpose of these studies the SPI-i variable, originally introduced by Chularojanamontri et al in 2013, was modified in order to eliminate disease duration as a confounder and increase the weighting of previous interventions. This involved the elimination of the first two items of the SPI-i, which cover disease duration (see figure 3.2). The SPI-i variable was recoded and scored out of 8 as opposed to 10, as in the original version.

3.5.3 Data management for study one

All data from the primary care cohort was entered into an open source clinical data management system (CDMS) and exported into a Microsoft Excel spreadsheet. The data from the secondary care cohort was processed by me following each study visit. All data was recorded on an excel spreadsheet. Upon completion of data collection the two data sources were merged and a data cleaning process was implemented prior to any statistical analyses. Any missing observations were coded as 960 or 99999 depending on the upper limit for the variable. The data was then exported into IBM SPSS statistics for analysis.

3.5.4 Data analyses for study one

(Data presented in chapter four)

Descriptive statistics were used to summarise variables, with the median and inter-quartile range (IQR) given for non-normal continuous variables and percentages for categorical variables. The impact of physical activity levels on cardiovascular risk factors in psoriasis was assessed using chi-square tests.

Spearman correlations were used to determine relationships between PASI and the IPAQ, the DLQI and the IPAQ and the SPI-p and SPI-i components of the SPI and IPAQ. The Kruskal-Wallis test was used to determine any significant differences in PASI across the 3 levels of activity (categorical IPAQ score) and also the SPI-p across the 3 activity levels. An additional analysis was carried out using the modified SPI-i; Mann-Whitney tests were performed to detect any differences in the IPAQ scores for those who had received no interventions (coded as 0) and those who had received 1 or more interventions (coded as 1).

The guidelines provided by the AHA (see Section 1.8.5 for details), were used in the analysis for this study as a standard measure of physical activity. As described in Section 3.5.2, a new variable was created by adding together the individual scores for moderate and vigorous-intensity activity. Individuals who met the criteria stated by the AHA were then recoded as 1 and those who did not meet the guidelines were recoded as 2. Independent samples T tests were used to assess differences in PASI, modified SPI-i and SPI-p scores between those who did adhere to the guidelines for physical activity and those who did not.

Following on from the correlation analysis with the DLQI and IPAQ, 6 items from the DLQI were selected for further investigation (described in section 3.5.2). It was decided that items 1, 2, 4, 5, 6 and 10 of the DLQI were the most relevant for examining psoriasis-specific barriers to physical activity. These items explored the following factors: skin sensitivity, embarrassment, clothing choices, social/leisure activities, engagement in sport and treatment (see table 3). The original 4 response options were recoded into 0 '*not at all,' 'a little,'* or 1 *'a lot,'* or *'very much*'. Independent samples T tests were used to compare individuals who scored 0 and 1 for each of the selected DLQI items in terms of: overall IPAQ scores and individual scores for walking, moderate and vigorous-intensity physical activity. Chi-square tests were then used to determine significant differences between those who do adhere to the AHA guidelines for physical activity and those who do not, in terms of their responses to the chosen DLQI questions.

Multiple linear regression analysis was used to determine which of the chosen DLQI items (if any) were the best predictors of physical activity. Four multiple regression models were constructed with total IPAQ scores, walking scores, moderate intensity physical activity scores and vigorous-intensity activity scores as the corresponding dependent variables. The independent variables in each model included: age, sex,

age of onset of psoriasis, disease duration and the 6 chosen items of the DLQI. The DLQI variables were entered into each model as continuous variables.

3.6 Study two: Is the International Physical Activity Questionnaire associated with arterial stiffness and cardiorespiratory fitness in patients with psoriasis?

3.6.1 Overview

242 participants were recruited from primary and secondary care to this study. This work interrogated hypothesis ii) *self-report physical activity provides a valid indication of cardiorespiratory fitness and potential CVD risk in patients with psoriasis* (see section 2.2).

Study two assessed the relationship between pulse wave velocity (PWV: a pre-clinical marker of future cardiovascular events) and diastolic reflection area (DRA: a proposed measure of cardiorespiratory fitness). This study also evaluated the the relationship between arterial stiffness (PWV) and self-reported levels of physical activity. Additionally, this study explored whether self-report physical activity was a valid measure of activity levels when compared to an objective measure of cardiorespiratory fitness (DRA) in patients with psoriasis. Finally, study two determined whether the PWV and DRA parameters provided a valid indication of self-report sedentary behaviour.

This section will provide a more detailed overview of the assessments used in Study 2 of this PhD. An example copy of an arteriograph can be found in appendix one. There will also be a subsection providing details of the statistical analysis.

3.6.2 Study two assessments

PWV

During the second study visit, assessment of PWV and DRA was made using the Tensiomed arteriograph. The arteriograph measures a range of arterial function parameters, including aortic PWV and DRA, which were the two primary variables used in this study. The aortic PWV provides information on the possible rigidity of the aorta.

The TensioMed software is windows-based software consisting of two components: the patient and user database and the device component which allows for device setup, download and evaluation of the data. The TensioMed arteriograph uses the distance from the suprasternal notch (jugulum) to the pubic symphysis to reflect the distance travelled by the pulse wave. The distance between these two sites is measured along the body surface (in centimetres) with the patient in the supine position. This measurement is then inputted into the software. The TensioMed arteriograph uses a similar method as is what is used for blood pressure, in that a cuff is placed tightly around the patient's dominant arm. The hose of the cuff is then connected to the pneumatic connector on the left-hand side of the device. In the first phase a blood pressure measurement is recorded and in the second phase a pulse waveform analysis is performed. Initially the device inflates back to the measured diastolic value and registers the pulse waves for a previously determined duration (8 seconds by default). Secondly, the device inflates further to the suprasystolic value (define as the measured systolic value + 35mmHg) which occludes the brachial artery completely and registers the pulse waves for 8 seconds (by default). An arteriograph report, containing the PWV value, appears on the computer screen when the examination is complete (TensioMed).

PWV Validation

A small substudy was carried out in order to assess both intra-operator and inter-operator variability in the jugulum-symphysis measurements within the primary care group of participants. A single individual therefore measured the jugulum-symphysis for each participant.

A total of 69% of the original primary care cohort returned to have their jugulum-symphysis remeasured. The results from the remeasure revealed a large degree of variability. This indicated that, in some cases, the jugulum-symphysis measurements may not have been performed correctly. PWV values were then recalculated for the 69% of participants who returned, using their remeasured jugulum-symphysis. Subsequently, a decision was made to take the 'new' PWV measurements forward into the analyses.

Diastolic Reflection Area

The DRA is a dimensionless index which provides information about the quality of diastolic filling condition of the left coronary artery during diastole. The higher the DRA value, the better the filling condition of the left coronary artery during diastole. The DRA is also thought to provide information about cardiac fitness. Very little data have been published on the DRA.

3.6.3 Data management for study two

The data for this study was collected alongside the data for study one and was stored in the same format. See section 3.5.3 for details on data management.

3.6.4 Data analysis for study two

(Data presented in chapter five)

Descriptive statistics were used to summarise variables, with the median and inter-quartile range (IQR) given for non-normal continuous variables. Spearman correlations were used to assess the relationship between PWV and DRA, PWV and the IPAQ and DRA and the IPAQ (including the total IPAQ scores and the individual scores for walking, moderate and vigorous-intensity activities). The same test was also used to examine the relationship between sedentary behaviour and both PWV and DR. Sedentary behaviour was assessed by a single item on the IPAQ.

The Kruskal-Wallis test was used to determine any significant differences in PWV values across the 3 levels of activity (categorical IPAQ score) and also the DRA across the 3 activity levels. In order to determine which of the three groups were significantly different from one another, a post-hoc analysis was performed using the Dunn-Bonferroni test (a non-parametric, pairwise multiple-comparisons procedure).

Independent samples T tests were used to assess differences in both PWV and DRA values between those who did adhere to the AHA guidelines for physical activity and those who did not. See section 3.5.4 for details regarding coding of the AHA data.

Finally, two hierarchical regression models were constructed for PWV and DRA, respectively, with each of these variables as the dependent variable. The purpose of constructing these models was to see whether self-report physical activity was a significant predictor of PWV and/or DRA whilst controlling for various confounding demographic factors.

3.7 Study three: Can the biochemical profile of patients with psoriasis provide an indication of physical activity levels and arterial stiffness?

3.7.1 Overview

117 participants were recruited from secondary care to this study. This work interrogated hypothesis iii) *biomarkers for vascular dysfunction are indicative of cardiorespiratory fitness and arterial stiffness in patients with psoriasis* (see section 2.2).

Study three explored the relationship between self-report physical activity and the biochemical profile (including sE-selectin, metabolic markers, adipokines, circulatory lipids and inflammatory markers) of patients with psoriasis. Additionally, the relationship between biochemical profile and, a) arterial stiffness (PWV), b) cardiorespiratory fitness (DRA) and c) physical severity of psoriasis, as measured by the PASI was also assessed in study three.

Furthermore, study three determined whether physical activity was a significant predictor of the biochemical profile of people with psoriasis, even when controlling for demographic factors and psoriasis severity measures. Finally, this study assessed whether the biochemical profile of patients with psoriasis and/or their physical activity levels were predictive of a) their arterial stiffness (PWV) and b) their DRA, even when controlling for demographic factors and psoriasis severity measures.

This section will provide a more detailed overview of the ELISA method used to analyse the plasma levels of IL-6, TNF-α, E-selectin, resistin, leptin, adiponectin and hs-CRP. The analysis of these markers was performed by me at the Specialist Assay Lab in the Manchester Royal Infirmary. Analysis of fasting glucose, insulin, HbA1C and lipids was made by the biochemistry lab at Salford Royal Hospital. There will also be a subsection providing details of the statistical analysis.

3.7.2 Study three assessments

Sample collection

Venous blood was collected into EDTA blood tubes. Centrifugation of blood samples (1800 rpm for 15 minutes), which allowed separation and collection of plasma, was performed within 2 hours of venepuncture. Plasma samples were stored at -80°C until required.

Enzyme-linked immunosorbent assay technique

DuoSet ELISA development kits for IL-6, TNF-α, sE-selectin, resistin, leptin and adiponectin were obtained from research and development systems (Abingdon, UK). The ELISA technique used in this study is based on the antibody sandwich principle.

First, a capture antibody in phosphate-buffered saline (PBS) was added to a microtitre plate and incubated overnight at room temperature (RT) to create a solid phase. After a standard washing step (with 0.05% tween-20 in PBS, x3), the plate was blocked by incubation for 1 hour with reagent diluent (1% bovine serum albumin in PBS). After a further washing step (x3) standards and samples were then incubated for 2 hours with the solid phase antibody which captures the antigen.

After washing (x3), biotin-labelled detection antibody was added and incubated for 1hour. After further washing (x3), streptavidin-peroxidase was added and incubated for 30minutes. A final washing step (x3) was carried out and a substrate

Tetramethylbenzidine (TMB, Sigma-Aldrich, Poole, Dorset) solution was added and colour developed in proportion to the amount of bound analyte. Colour development was stopped by the addition of a 'stop' solution, which in this case was 1 molar sulphuric acid. Colour intensity was then measured at 450 nanometres (nm) on a plate reader (Dynex Technologies, Worthing, UK). Finally, a standard curve was generated using Fig P software (Hamilton, ON, Canada) and concentrations of biomarker in serum were calculated.

A similar methodology was applied to all biomarkers, although the conjugates used varied according to the biomarker being assayed as well as the standards employed to ascertain inter-plate variability.

3.7.3 Data management for study three

Following each assay, the concentrations of biomarker in serum were calculated and recorded on a Microsoft Excel spreadsheet. Any missing observations were coded as 99999. The data was then exported into IBM SPSS statistics for analysis.

3.7.4 Data analysis for study three

(Data presented in chapter six)

Descriptive statistics were used to summarise variables, with the median and inter-quartile range (IQR) given for non-normal continuous variables. Spearman correlations were used to determine the presence of significant relationships between self-reported physical activity (including the total IPAQ scores and the individual scores for walking, moderate and vigorous-intensity activities) and the blood biomarkers.

The independent samples t-test was used to assess differences in the levels of each biomarker between those who met the AHA guidelines for physical activity and those who did not. See section 3.5.4 for details regarding coding of the AHA data.

Subsequently, Spearman correlations were used to detect the presence of significant relationships between PASI and the blood biomarkers.

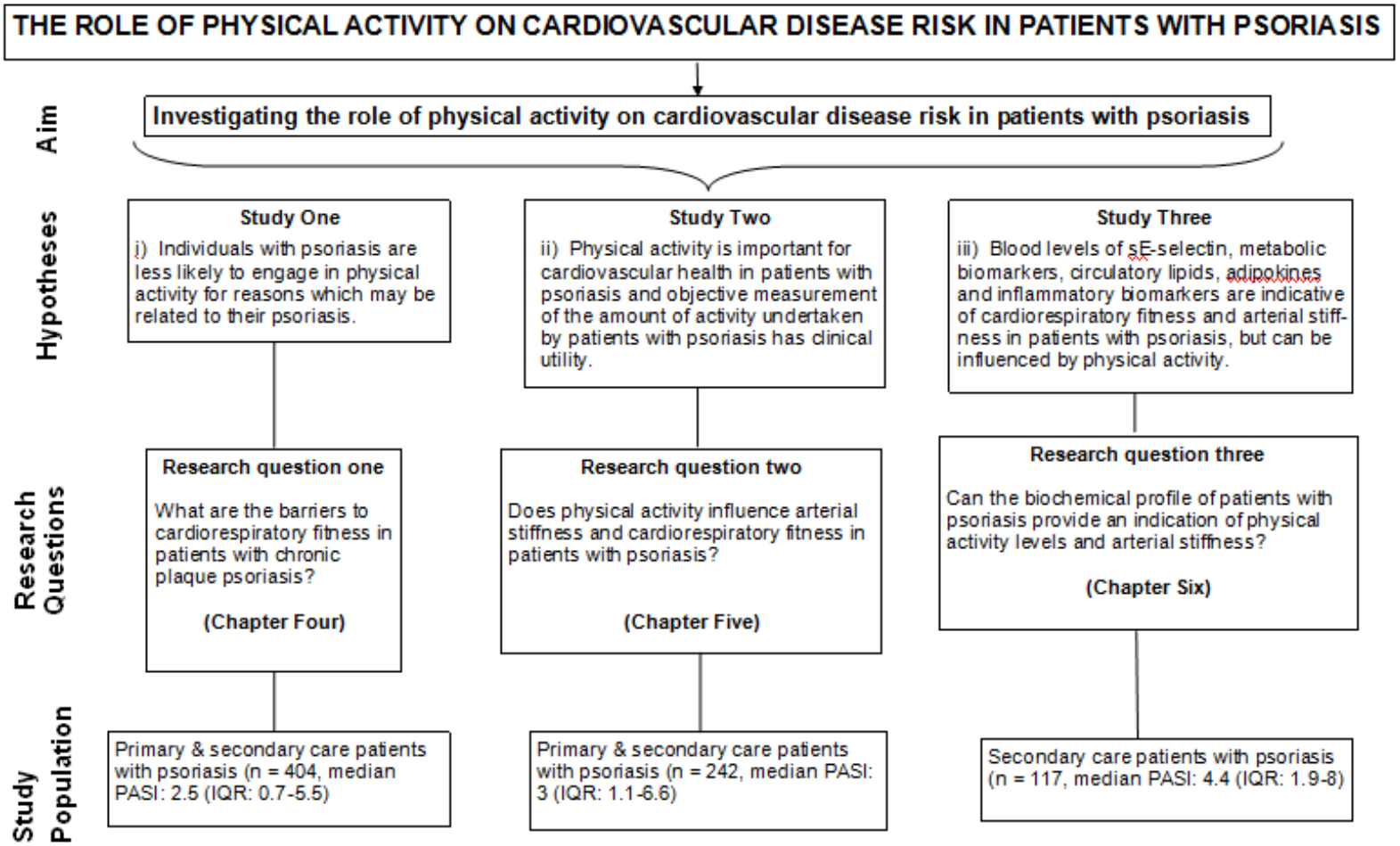
Spearman correlations were also used to identify the presence of significant relationships between PWV (arterial stiffness) and the blood biomarkers. The same test was then used to determine significant correlations between DRA (measure of cardiac fitness) and the blood biomarkers which were chosen for the analysis (see section 6.4 for a list of the chosen biomarkers).

The biomarkers which were found to correlate with physical activity were entered into hierarchical multiple regression analyses. The purpose of this was to determine whether the variable of interest was able to explain some of the remaining variance in the dependent variable when statistically controlling for various other independent variables. In this instance, a hierarchical regression model was constructed for each biomarker, with the biomarker as the dependent variable. The independent variables which were entered into each model included demographic factors, psoriasis severity measures and physical activity.

For the analyses described above, people with diabetes and those on lipid lowering medication were excluded from the analyses of metabolic markers and circulatory lipids. Additionally, all of the analyses described above were repeated in a sensitivity analysis excluding participants with psoriatic arthritis. Any changes to the original results, upon exclusion of psoriatic arthritis, are presented accordingly in chapter six of this thesis. In the hierarchical multiple regression analyses, psoriatic arthritis was entered as an independent variable.

Biomarkers which were found to correlate with PWV were also taken forward for hierarchical multiple regression analysis. In this instance, PWV was entered into the model as the dependent variable. The independent variables which were entered into this model included demographic factors, psoriasis severity measures, physical activity scores and biomarker concentrations (only those biomarkers which were found to correlate with PWV in previous analyses). A similar model was also constructed for DRA. In these models, people with diabetes, those on lipid lowering medication and those with psoriatic arthritis were also entered as independent variables.

Figure 3.3 An overview of the aim, hypotheses, research questions and study populations for each of the three studies comprising this PhD.



CHAPTER FOUR: WHAT ARE THE BARRIERS TO CARDIORESPIRATORY FITNESS IN PATIENTS WITH CHRONIC PLAQUE PSORIASIS?

4.1 Hypothesis

Individuals with psoriasis are less likely to engage in physical activity for reasons which may be related to their psoriasis.

4.2 Rationale

Patients with psoriasis often exhibit avoidance coping, which may result in people avoiding physical activity (Fortune et al., 1997a, Fortune et al., 2003).

Emerging evidence suggets that psoriasis may present a barrier to making health promoting lifestyle choices, such as engagement in physical activity (Naldi et al., 2014, Torres et al., 2014, Wilson et al., 2012). Despite widespread speculation that decreased physical activity in patients with psoriasis is consequent upon disease severity or is related to psychological barriers, the objective evidence is limited. However, investigation of physical activity, using suitable assessment tools, in conjunction with identification of barriers to physical activity in patients with psoriasis remains unexplored.

Additionally, there are no guidelines in place at present which specifies how to deal with the management of cardiovascular risk in psoriasis patients (González-Gay et al., 2012). In the context of physical activity, this is because the relationship between

physical activity, specifically the type (intensity) or duration of physical activity and cardiometabolic risk has not been assessed.

4.3 Results

The cohort of participants for this study was divided on the basis of gender and age. The reason for this was the AHA guidelines for physical activity have established different criteria for individuals aged between 18-65 and for individuals over the age of 65, therefore I felt it was important to assess the two age groups separately. Additionally, the Health Survey England identified varying patterns of physical activity between males and females and so I also chose to look at these groups separately. The purpose of this study was to identify the barriers to physical activity in patients with psoriasis, and so by dividing the cohort into these different groups it allowed me to focus my analysis and identifiy age and gender-specific psoriasis related barriers to physical activity.

4.3.1 Subject characteristics

Of the 404 subjects who took part, a median age of 49 was observed (IQR: 38-61) with 46.9% males and 53.1% females. Additionally, 54.7% of participants had a family history of the psoriasis. The median PASI was 2.5 (0.7-5.5). Table 4.3.1 presents the characteristics of participants in this study. The median and IQR are presented for continuous variables and percentages are presented for categorical variables.

Table 4.3.1 Characteristics of study subjects.

	Study group one (n=404)	18-65's (n=336)	Over 65's (n=68)	All males (n=189)	Males 18-65 (n=154)	Males over 65 (n=28)	All females (n=215)	Females 18-65 (n=171)	Females over 65 (n=33)
Age	49 (38-61)	45 (36-54)	71 (67-77)	49 (39-63)	44 (36-52)	71 (67-77)	50 (37-61)	46 (35-55)	72 (68-76)
Age of psoriasis onset	23 (14-35)	20 (14-32)	40.5 (25-60)	25 (16-35)	22 (15-32)	40 (28-64)	21 (13-36)	20 (13-32)	45 (20-59)
Disease Duration	20 (11-32)	19 (11-30)	30 (15-47)	19 (10-32)	18 (10-29)	32 (13-47)	22 (11-32)	21 (11-30)	26 (15-53)
Family history of psoriasis (%)	54.7	58	38.5	51.9	57.3	27.3	57.2	58.5	50
BMI	27.8 (24.5-31.6)	27.9 (24.6-31.9)	27 (24-31)	28 (25-31.4)	28 (25-31.4)	27.7 (25.3-31.5)	27.6 (24-31.7)	27.7 (24-32.3)	27 (23-30)
Smoking (%)	31.4	34.6	10.8	25.8	29.6	13	35.9	39.1	7.1
Hypertension (%)	29.1	24.3	52.9	29.1	23.4	54.3	29.1	25	51.5
Diabetes (%)	6.5	5.1	13.2	7.4	4.5	20	5.6	5.6	6.1
Atrial fibrillation (%)	5.2	3.6	13.2	6.9	3.9	20	3.8	3.3	6.1
Angina (%)	4	2.1	13.2	5.8	3.9	14.3	2.3	0.6	12.1
PASI	2.5 (0.7-5.5)	2.7 (0.8-6)	1.8 (0.3-3.3)	3.4 (0.8-7)	3.7 (1.2-7.8)	1.6 (0.3-4.4)	2.1 (0.5-4.2)	2.2 (0.6-4.7)	1.9 (0.3-2.9)
DLQI	4 (1-7)	4 (1-8)	2 (1-5)	3 (1-8)	4 (2-8)	1 (1-5)	4 (1-7)	4 (1-7)	4 (1-6)
Walking (MET-mins/week)	792 (272.3-2079)	742 (297-2079)	1188 (264-2772)	990 (297-2772)	792 (297-2376)	1188 (264-2772)	693 (264-1732.5)	693 (264-1584)	981.8 (285-2004.8)
Moderate activity (MET-mins/week)	0 (0-720)	0 (0-720)	0 (0-480)	160 (0-960)	180 (0-960)	140 (0-1590)	0 (0-480)	0 (0-480)	0 (0-120)
Vigorous activity(MET-mins/week)	0 (0-960)	0 (0-1090)	0 (0-720)	100 (0-1560)	240 (0-1650)	0 (0-1200)	0 (0-920)	0 (0-960)	0 (0-360)
Total IPAQ (MET-mins/week)	1767 (594-4068)	1823.3 (639.8-4102.5)	1414 (457-4068)	2157.8 (698.3-4525.5)	2157.8 (710.8-4540.5)	2395.8 (615-4564.5)	1529.3 (459.5-3154.5)	1584 (491.3-3467.3)	1065 (297-1899.8)
Category 1 (%)	27.4	26.5	32.1	21.3	20.7	24.1	33	31.6	40.7
Category 2 (%)	32.8	32.6	33.9	36.1	36.4	34.5	29.7	29.1	33.3
Category 3 (%)	39.8	40.9	33.9	42.6	42.9	41.4	37.3	39.2	25.9

Table 4.3.2 Impact of physical activity on cardiovascular risk factors in psoriasis.

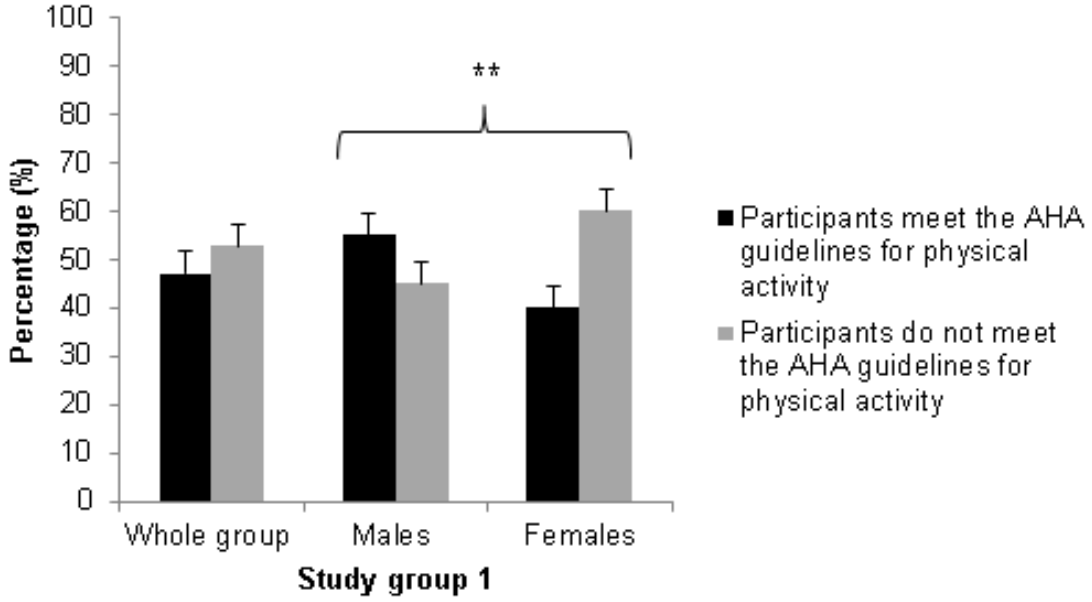
Risk factors	**'Unhealthy' (n=188)**	**'Health-promoting' (n=168)**	**P value**
Hypertension (29.1%)	19.2	9.9	**0.003**
Diabetes (5.9%)	5.1	0.8	**0.004**
Obesity (71.3%)	40.3	31	**0.045**
Smoking (30.5%)	14.6	15.9	0.484
Atrial fibrillation (5.1%)	3.7	1.4	0.154
Angina (4.2%)	2.5	1.7	0.778

'Unhealthy' = participants who did not meet the AHA guidelines for physical activity. 'Health-promoting' = participants who adhere to the guidelines for physical activity. Statistically significant values from the chi-square tests are highlighted in bold. Missing data = 12%.

4.3.2 Over 50% of patients with psoriasis engaged in less than the recommended amount of physical activity for cardiorespiratory fitness

In a previous study by Torres et al (Torres et al., 2014) it was observed that an alarming 18.9% of patients with psoriasis failed to meet the guidelines for physical activity (n=90). However, in our much larger population it was revealed that 52.8% (45% of males and 60% of females) of patients with psoriasis failed to meet the recommended guidelines for physical activity, provided by the AHA. A chi-square test showed that the proportion of females who did not meet the guidelines for physical activity was significantly greater than the proportion of males (P = 0.007). These results are summarised in figure 4.3.2.1.

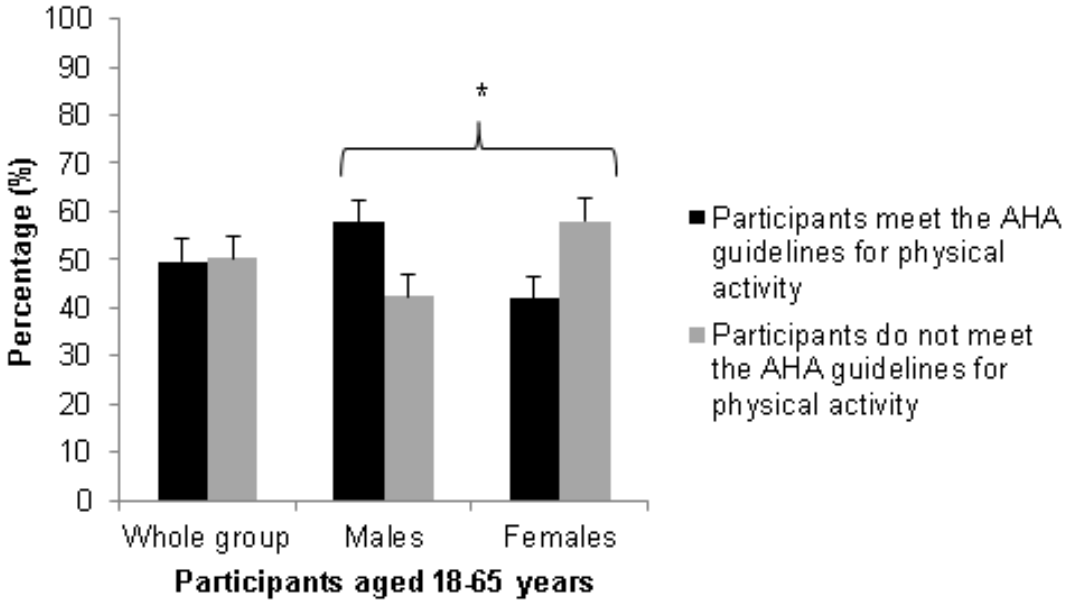
Figure 4.3.2.1 Over 50% of patients with psoriasis (including individuals aged 18-65 and those over 65 and males and females) engaged in less than the recommended weekly amount of physical activity (n = 356)



*The bar graph highlights the proportion of participants who meet the AHA guidelines for physical activity and those who do not meet the guidelines. 52.8% of study group 1 did not meet the guidelines. It was found that the proportion of females who did not meet the guidelines for physical activity (60%) was significantly greater than the proportion of males (45%). Statistical analysis: chi-square test, **P<0.001, (11.9% missing data).*

Subsequently, participants aged between 18 and 65 years were assessed. It was found that 50.3% (42.3% of males and 58% of females) of patients aged 18-65 did not meet the AHA guidelines for physical activity. A chi-square test also showed that the proportion of females who did not meet the guidelines for physical activity was significantly greater than the proportion of males (P = 0.011). These results are summarised in figure 4.3.2.2.

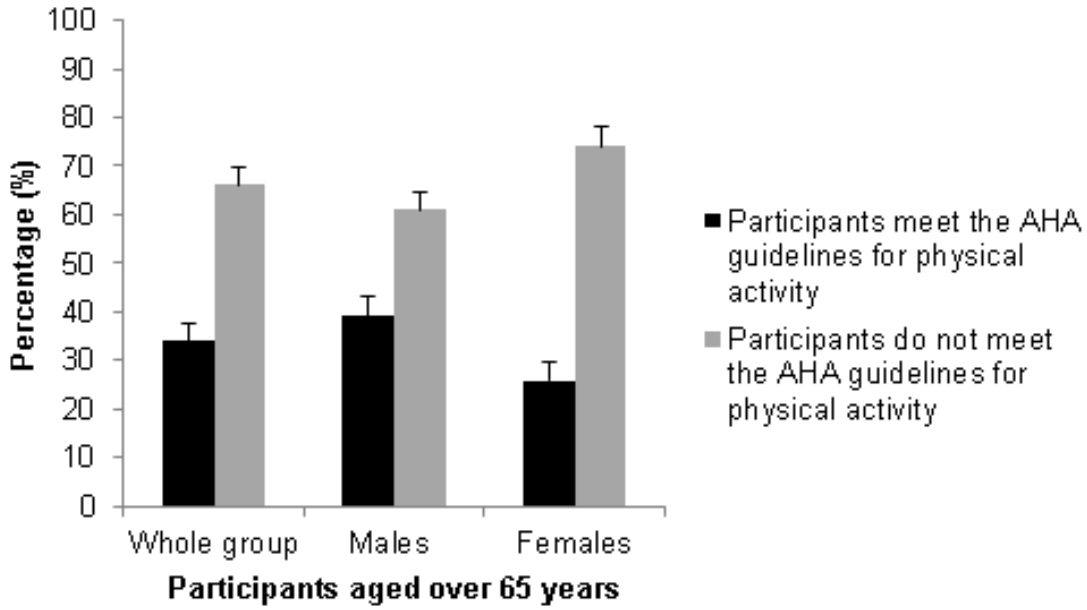
Figure 4.3.2.2 Over 50% of patients with psoriasis, aged between 18-65 years, engaged in less than the recommended weekly amount of physical activity (n = 300)



*The bar graph highlights the proportion of participants, aged 18-65, who meet the AHA guidelines for physical activity and those who do not meet the guidelines. 50.3% of patients aged 18-65 years did not meet the guidelines. It was found that the proportion of females who did not meet the guidelines for physical activity (58%) was significantly greater than the proportion of males (42.3%). Statistical analysis: chi-square test, *P<0.05, (10.7% missing data).*

Finally, participants over the age of 65 were examined. It was found that 66.1% (60.9% of males and 74.1% of females) of patients, over the age of 65 year did not meet the AHA guidelines for physical activity. A chi-square test showed no significant difference in the proportion of males and females, within this age group, who failed to meet the AHA guidelines for physical activity. The results for participants over the age of 65 are summarised in figure 4.3.2.3.

Figure 4.3.2.3 Over 66% of patients with psoriasis, over the age of 65 years, engaged in less than the recommended weekly amount of physical activity (n = 56)



The bar graph highlights the proportion of participants, over the age of 65, who meet the AHA guidelines for physical activity and those who do not meet the guidelines. 66.1% of patients over the age of 65 did not meet the guidelines. No significant difference in the proportion of males and females, within this age group, who failed to meet the AHA guidelines for physical activity, was observed. Statistical analysis: chi-square test, (missing data: 17.6%).

There was no significant difference in the proportion of males and females who met the guidelines for physical activity in the over 65 group. This may have been due to having a small sample size within this age group. Additionally, it could be that age- related barriers are impacting on levels of physical activity in both males and females over the age of 65, hence why such a large percentage of these individuals are failing to adhere to the guidelines.

4.3.3 Are low levels of physical activity in patients with psoriasis associated with disease severity?

The purpose of these analyses was to assess the relationship between psoriasis severity, as measured by the DLQI, PASI and SPI.

4.3.3.1 The greater the impact psoriasis has on quality of life, the less likely people are to engage in physical activity

A Spearman's rho correlation analysis was used to assess the relationship between the DLQI and the IPAQ (the mean overall score was used for each variable). A weak but statistically significant negative correlation between physical activity and total DLQI scores was observed ($r = -0.109$, $p = 0.049$).

The results from this analysis formed the basis of subsequent analyses which focuses on the psoriasis-specific barriers to physical activity.

4.3.3.2 Psoriasis-specific experiences can impact significantly on levels of physical activity

Items 1, 2, 4, 5, 6 and 10 of the DLQI were selected as the most relevant for examining psoriasis-specific barriers to physical activity. These items explored the following factors: skin sensitivity, embarrassment, clothing choices, social/leisure activities, engagement in sport and treatment. Prior to carrying out the analyses presented in this section, a subanalysis (using Spearman correlations) was conducted (using the whole study group), in order to validate the use of these specific items from the DLQI. The results from this analysis revealed weak significant inverse correlations between the composite DLQI scores and the scores for physical activity (as assessed by the IPAQ). More specifically, relationships were observed between the following variables: DLQI item 1 and vigorous intensity activity (r = -0.171, p=0.001); DLQI item 2 and total IPAQ score (r = -0.113, p-0.041); DLQI item 4 and vigorous intensity activity (r = -161, p=0.002); DLQI item 5 and vigorous intensity activity (r = -0.112, p=0.034); and DLQI item 10 and vigorous intensity activity (r = -0.107, p=0.007). There was no significant correlations observed between DLQI item 6 and activity, however, it was decided to keep this item in the analysis as it asks specifically about sporting activities, which was relevant to the overall research question.

For the purpose of the primary analysis the original four response options to the items of the DLQI were recoded into 0 '*not at all,' 'a little,'* or 1 *'a lot,'* or *'very much*'. Independent samples T tests were used to compare individuals who scored 0 and 1 for each of the selected DLQI items in terms of: overall IPAQ scores and individual scores for walking, moderate and vigorous-intensity physical activity.

Upon examination of study group 1 as a whole it was observed that skin sensitivity (item 1), clothing choice (item 4), social/leisure activities (item 5) and treatment (item

10) significantly influenced levels of vigorous-intensity physical activity. Participants who responded with ‘a lot’ or ‘very much’ to these items of the DLQI had significantly lower scores for vigorous-intensity physical activity compared to those who responded with ‘not at all’ or ‘a little.’ Table 4.3.3 summarises these significant results.

Table 4.3.3 Summary of the statistically significant results for the study one cohort as a whole.

	Item 1	**Item 4**	**Item 5**	**Item 10**
Vigorous-intensity Activity	0 M=1141, 1 M=567; t=2.97, p=0.003	0 M=1054, 1 M=632; t=2.18, p=0.031	0 M=1038, 1 M=420; t=2.5, p=0.017	0 M=1080, 1 M=594; t=2.24, p=0.027

0 M=mean IPAQ score for those who responded with ‘not at all’ or ‘ a little’ to items of the DLQI (units: MET-mins/week); 1 M=mean IPAQ score for those who responded with ‘a lot’ or ‘very much’ to items of the DLQI (units MET-mins/week); t=t value; p=significance value.

In participants aged between 18 and 65 years it was observed that skin sensitivity (item 1) and participation in social/leisure activities (item 5) were factors which significantly impacted on people's engagement in vigorous-intensity physical activity. Table 4.3.4 summarises these significant results.

Table 4.3.4 Summary of the statistically significant results for participants aged 18-65.

	Item 1	**Item 5**
Vigorous-intensity activity	0 M=1108, 1 M=622; t=2.29, p=0.023	0 M=1055, 1 M=476; t=2.07, p=0.045

0 M=mean IPAQ score for those who responded with 'not at all' or ' a little' to items of the DLQI (units: MET-mins/week); 1 M=mean IPAQ score for those who responded with 'a lot' or 'very much' to items of the DLQI (units MET-mins/week); t=t value; p=significance value.

In participants over the age of 65 it was found that self-consciousness and feelings of embarrassment about their skin (item 2) along with participation in social/leisure activities (item 5) were factors which significantly impacted on their engagement in mild-intensity physical activity (walking). Additionally, it was observed that skin sensitivity (item 1) and clothing choice (item 4) were factors which significantly impacted on their engagement in both moderate and vigorous-intensity physical activity. Table 4.3.5 summarises these significant results.

Table 4.3.5 Summary of the statistically significant results for participants over the age of 65.

	Item 1	**Item 2**	**Item 4**	**Item 5**
Walking	ns	0 M=1621, 1 M=380; t=3.67, p=0.008	Ns	0 M=1597, 1 M=739; t=2.46, p=0.033
Moderate-intensity Activity	0 M=730, 1 M=95; t=3.1, p=0.003	Ns	0 M=760, 1 M=24; t=3.43, p=0.001	Ns
Vigorous-intensity Activity	0 M=1310, 1 M=222; t=2.66, p=0.01	Ns	0 M=983, 1 M=87; t=2.4, p=0.021	Ns

0 M=mean IPAQ score for those who responded with 'not at all' or ' a little' to items of the DLQI (units: MET-mins/week); 1 M=mean IPAQ score for those who responded with 'a lot' or 'very much' to items of the DLQI (units MET-mins/week); t=t value; p=significance value.

Upon examination of male participants it was found that participation in social/leisure activities (item 5) was a factor which significantly impacted on their engagement in mild-intensity physical activity (walking). Table 4.3.6 summarises these significant results.

Table 4.3.6 Summary of the statistically significant results for male participants.

	Item 5
Walking	0 M=1531, 1 M=963; t=2.11, p=0.044

0 M=mean IPAQ score for those who responded with 'not at all' or ' a little' to items of the DLQI (units: MET-mins/week); 1 M=mean IPAQ score for those who responded with 'a lot' or 'very much' to items of the DLQI (units MET-mins/week); t=t value; p=significance value.

In male participants aged between 18 and 65 it was found that none of the chosen factors from the DLQI significantly impacted on physical activity scores.

In males over the age of 65 it was observed that self-consciousness and feelings of embarrassment about their skin (item 2) were factors which significantly impacted on their engagement in vigorous-intensity physical activity. Table 4.3.7 summarises these significant results.

Table 4.3.7 Summary of the statistically significant results for male participants over the age of 65.

	Item 2
Vigorous-intensity activity	0 M=1872, 1 M=0; t=2.88, p=0.01

0 M=mean IPAQ score for those who responded with 'not at all' or ' a little' to items of the DLQI (units: MET-mins/week); 1 M=mean IPAQ score for those who responded with 'a lot' or 'very much' to items of the DLQI (units MET-mins/week); t=t value; p=significance value.

Upon examination of female participants it was found that the impact of their skin on their participation in sport (item 6) was a factor which significantly impacted on their total IPAQ score as well as their score for moderate-intensity physical activity. Additional factors, along with item 6, including skin sensitivity (item 1) and participation in social/leisure activities (item 5), were also found to significantly impact female engagement in vigorous-intensity physical activity. Table 4.3.8 summarises these significant results.

Table 4.3.8 Summary of the statistically significant results for female participants.

	Item 1	Item 5	Item 6
Total IPAQ score	Ns	Ns	0 M=2411, 1 M=234; t=8.31, p=<0.001
Moderate-intensity activity	Ns	Ns	0 M=449, 1 M=0; t=5.87, p<0.001
Vigorous-intensity activity	0 M=904, 1 M=404; t=2.4, p=0.018	0 M=809, 1 M=160; t=3.87, p=<0.001	Ns

0 M=mean IPAQ score for those who responded with 'not at all' or ' a little' to items of the DLQI (units: MET-mins/week); 1 M=mean IPAQ score for those who responded with 'a lot' or 'very much' to items of the DLQI (units MET-mins/week); t=t value; p=significance value.

Similarly, in females aged between 18 and 65 years it was found that the impact of their skin on their participation in sport (item 6) was a factor which significantly impacted on their total IPAQ score as well as their score for moderate-intensity physical activity. Additional factors, as well as item 6, including skin sensitivity (item 1), self-consciousness and feelings of embarrassment about their skin (item 2) and participation in social/leisure activities (item 5), were also found to significantly impact engagement in vigorous-intensity physical activity in females aged 18-65. Table 4.3.9 summarises these significant results.

Table 4.3.9 Summary of the statistically significant results for female participants aged 18-65.

	Item 1	Item 2	Item 5	Item 6
Total IPAQ Score	NS	NS	NS	0 M=2561, 1 M=234; t=7.9, p<0.001
Moderate-intensity Activity	NS	NS	NS	0 M=475, 1 M=0; t=5.53, p<0.001
Vigorous-intensity Activity	0 M=906, 1 M=294; t=3.03, p=0.003	0 M=844, 1 M=366; t=2.17, p=0.033	0 M=825, 1 M=185; t=3.5, p=0.001	NS

0 M=mean IPAQ score for those who responded with 'not at all' or ' a little' to items of the DLQI (units: MET-mins/week); 1 M=mean IPAQ score for those who responded with 'a lot' or 'very much' to items of the DLQI (units MET-mins/week); t=t value; p=significance value.

In female participants over the age of 65 it was found that none of the chosen factors from the DLQI significantly impacted on physical activity scores.

Subsequently, chi-square tests were then used to determine significant differences between those who met the AHA guidelines for physical activity and those who did not, in terms of their responses to the chosen DLQI questions. Upon examination of study group 1 as a whole it was observed that skin sensitivity (item 1) was a factor which significantly impacted on whether patients met the AHA guidelines for physical activity or not (chi-square value: 5.05, p=0.025). Participants who responded with 'a lot' or 'very much' to item 1 of the DLQI were less likely to adhere to the guidelines for physical activity compared to those who responded with 'not at all' or 'a little.'

Similarly, in participants aged between 18 and 65 years it was also found that skin sensitivity (item 1) was a factor which impacted significantly on whether patients met the AHA guidelines for physical activity or not (chi-square value: 4.99, p=0.025).

In participants over the age of 65 years it was found that clothing choice (item 4) was a factor which impacted significantly on whether people adhered to the AHA guidelines for physical activity (chi-square value: 5.74, p=0.017).

Upon examination of all of the males in study group 1, it was found that none of the chosen factors from the DLQI significantly impacted on whether or not participants met the AHA guidelines for physical activity. The same result was also observed within the two age groups (males 18-65 and males over 65).

Upon examination of the female participants in study group 1, it was found that none of the chosen factors from the DLQI significantly impacted on whether or not participants met the AHA guidelines for physical activity. The same result was also observed in females aged 18-65 and in females over 65.

The results from these analyses are summarised in table 4.3.10.

Table 4.3.10 Summary of the participant groups which indicated significant relationships between chosen items on the DLQI and levels of physical activity.

DLQI	Item 1	Item 2	Item 4	Item 5	Item 6	Item 10
Over the last week:	how itchy, sore, painful or stinging has your skin been?	how embarrassed or self-conscious have you been because of your skin?	how much has your skin influenced the clothes you wear?	how much has your skin affected any social or leisure activities?	how much has your skin made it difficult to play sport?	how much of a problem has the treatment of your skin been, for example by making your home messy, or by taking up time?
Total IPAQ Score	No significant differences.	No significant differences.	No significant differences.	No significant differences.	All females (P=<0.001) Females 18-65 (P=<0.001)	No significant differences.
Walking	No significant differences.	Over 65's (P=0.008)	No significant differences.	Over 65's (P=0.033) All males (P=0.044)	No significant differences.	No significant differences.
Moderate-intensity physical activity	Over 65's (P=0.003)	No significant differences.	Over 65's (P=0.001)	No significant differences.	All females (P=<0.001) Females 18-65 (P=<0.001)	No significant differences.
Vigorous-intensity physical activity	Whole group (P=0.003) 18-65's (P=0.023) Over 65's (P=0.01) All females (P=0.018) Females 18-65 (P=0.003)	Males over 65 (P=0.01) Females 18-65 (P=0.033)	Whole group (P=0.031) Over 65's (P=0.021)	Whole group (P=0.017) 18-65's (P=0.045) All females (P=<0.001) Females 18-65 (P=0.001)	All females (P=<0.001) Females 18-65 (P=<0.001)	Whole group (P=0.027)
AHA guidelines	Whole group (P=0.034) 18-65's (P=0.036)	No significant differences.	Over 65's (P=0.044)	No significant differences.	No significant differences.	No significant differences.

The different participant groups are highlighted in colour: whole group (red), 18-65's (blue), over 65's (green), all males (orange), males over 65 (grey), all females (purple), females aged 18-65 (pink). No significant results were observed in males aged 18-65 and females over 65. Note: the over 65 groups are underpowered, due to the small numbers of patients within this age group.

4.3.4 Gender was the strongest predictor of physical activity in patients with psoriasis

The chosen six items from the DLQI were entered into a standard multiple regression analysis to determine both the size of the impact of these barriers on levels of physical activity and whether the impact was significant.

Four multiple regression models were constructed with total IPAQ scores, mild-intensity physical activity (walking), moderate-intensity physical activity and vigorous-intensity physical activity as the corresponding dependent variables. The responses to the chosen 6 items of the DLQI (see table 4.3.2 for the specific items) were entered into the models as continuous variables (see section 3.5.2 for details on scoring of the DLQI items) along with demographic factors including age, gender, disease duration and age of onset of psoriasis. Each of the dependent variables were initially transformed using the logarithm function in order to make them more 'normally' distributed, however, this did not affect the independent variables in the models and it did not improve the overall model fit. Therefore, the dependent variables were kept in their original format.

In the first regression model, total IPAQ score was entered as the dependent variable and the DLQI variables were entered as the independent variables along with demographic factors. The results generated from this analysis revealed an R^2 value of 0.07 indicating that this model explains 7% of the variance in total IPAQ scores. This result was shown to be significant as p was <0.05 (p=0.038). Gender was found to be a significant predictor of physical activity in this model (β-coefficient = -0.23, p = <0.0005). Table 4.3.4.1 summarises the β-coefficients for each independent variable.

Table 4.3.4.1 Results from the multiple linear regression with total IPAQ scores (n=328)

Predictor Variables	Beta	P value
Age	-0.404	0.32
Gender	**-0.230**	**<0.01**
Age of psoriasis onset	0.307	0.484
Disease duration	0.317	0.436
DLQI item 1	0.004	0.958
DLQI item 2	-0.071	0.408
DLQI item 4	0.072	0.436
DLQI item 5	-0.097	0.329
DLQI item 6	0.052	0.548
DLQI item 10	-0.068	0.379

Beta = Beta-coefficient. The R^2 value for this model was 0.07. Statistically significant values are highlighted in bold. Missing data: 18.8%.

In the second regression model, mild-intensity physical activity (walking) scores were entered as the dependent variable and the DLQI variables were entered as the independent variables along with demographic factors. The results generated from this analysis revealed an R^2 value of 0.025 indicating that this model explains 2.5% of the variance in mild-intensity activity scores (p=0.698). The β-coefficient values indicated that none of the independent variables were significant predictors of mild-intensity physical activity (walking) scores. Table 4.3.4.2 summarises the β-coefficients for each independent variable.

Table 4.3.4.2 Results from the multiple linear regression with mild-intensity physical activity scores (n=360)

Predictor Variables	Beta	P value
Age	0.009	0.981
Gender	-0.088	0.162
Age of psoriasis onset	0.012	0.978
Disease duration	-0.029	0.942
DLQI item 1	0.115	0.108
DLQI item 2	-0.058	0.49
DLQI item 4	0.085	0.355
DLQI item 5	-0.058	0.552
DLQI item 6	0.013	0.881
DLQI item 10	-0.130	0.089

Beta = Beta-coefficient. The R^2 value for this model was 0.025. Missing data: 10.9%.

In the third regression model, moderate-intensity physical activity scores were entered as the dependent variable and the DLQI variables were entered as the independent variables along with demographic factors. The results generated from this analysis revealed an R^2 value of 0.052 indicating that this model explains 5.2% of the variance in moderate-intensity activity scores (p=0.129). Gender was found to be a significant predictor of physical activity in this model (β-coefficient = -0.153, p = 0.015). Table 4.3.4.3 summarises the β-coefficients for each independent variable.

Table 4.3.4.3 Results from the multiple linear regression with moderate-intensity physical activity scores (n=364)

Predictor Variables	Beta	P value
Age	-0.605	0.127
Gender	**-0.153**	**0.015**
Age of psoriasis onset	0.559	0.191
Disease duration	0.564	0.156
DLQI item 1	0.005	0.942
DLQI item 2	-0.094	0.26
DLQI item 4	0.029	0.75
DLQI item 5	-0.152	0.117
DLQI item 6	0.153	0.111
DLQI item 10	0.063	0.405

Beta = Beta-coefficient. The R^2 value for this model was 0.052. Statistically significant values are highlighted in bold. Missing data: 9.9%.

In the final regression model, vigorous-intensity physical activity scores were entered as the dependent variable and the DLQI variables were entered as the independent variables along with demographic factors. The results generated from this analysis revealed an R^2 value of 0.044 indicating that this model explains 4.4% of the variance in moderate-intensity activity scores (p=0.221). Gender was found to be a significant predictor of physical activity in this model (β-coefficient = -0.133, p = 0.031). Table 4.3.4.4 summarises the β-coefficients for each independent variable.

Table 4.3.4.4 Results from the multiple linear regression with vigorous-intensity physical activity scores (n=376)

Predictor Variables	Beta	P value
Age	-0.08	0.839
Sex	**-0.133**	**0.031**
Age of psoriasis onset	-0.018	0.965
Disease duration	0.04	0.919
DLQI item 1	-0.081	0.248
DLQI item 2	-0.004	0.96
DLQI item 4	-0.041	0.65
DLQI item 5	-0.024	0.802
DLQI item 6	0.043	0.599
DLQI item 10	-0.038	0.61

Beta = Beta-coefficient. The R^2 value for this model was 0.044. Statistically significant values are highlighted in bold. Missing data: 6.9%.

The results from the multiple regression analyses indicated that gender was a significant predictor of physical activity, particularly moderate and vigorous-intensity physical activity, in patients with psoriasis. The R^2 value of each regression model was low, indicating that there are other external factors impacting levels of physical activity in this group of patients.

Taken together with the results presented in table 4.6.3, it is evident that barriers to physical activity in patients with psoriasis are both gender and psoriasis-specific. My results imply that females with psoriasis, specifically females aged between 18 and 65 years, are especially vulnerable.

4.3.5 The PASI is significantly inversely correlated with total IPAQ scores in females aged 18-65 years

Spearman correlation analyses were performed in order to assess the relationship between PASI and physical activity.

The results from this analysis revealed a significant, weak inverse correlation between PASI and total IPAQ scores in females aged between 18 and 65 years ($r = -0.187$, $p = 0.046$). Therefore, as PASI increased, the total IPAQ scores decreased. Lower IPAQ scores indicate lower levels of physical activity.

Subsequently, the Kruskal Wallis test was used to detect significant differences in PASI among the three categories of physical activity (categorical score of the IPAQ) in females aged between 18 and 65 years. The results from this analysis indicated no significant difference in PASI across the three levels of physical activity in this group of participants (mean ranks: low level of activity: 70.46, moderate level of activity: 59.57, high level of activity: 56.95; chi-square value: 3.22, $p = 0.2$). This may have been due to the lack of variation in PASI scores within the study population; low PASI scores throughout the study group may have made it difficult to detect significant differences.

Alternatively, this may have been due to misclassification of participants in the ‘high’ IPAQ category (category three) because although some individuals may fall into this category, their pattern of activity may not yield the health benefits in which the ‘high category is intended to represent. If a person has indicated that they take part in a large amount of mild-intensity activity, for example, walking for three hours seven days per week, this would generate an IPAQ score of 3780 MET-mins/week which means that they would fall into the ‘high’ level category.

Finally, an independent samples T test was used to assess differences in PASI between females aged 18-65 years who met the AHA guidelines for physical activity

and those who did not. The results from this test revealed no significant differences in PASI between those who met the guidelines for physical activity and those who did not (mean PASI: those who met the AHA guidelines = 2.8, those who did not meet the guidelines = 3.5; t = -0.977, p = 0.331).

The series of statistical analyses that was carried out on females aged 18-65 years (described above) were also performed on the other participant groups. However, no significant results were observed.

4.3.5.1 The intervention component of the SPI is negatively correlated with vigorous-intensity physical activity scores in females over the age of 65

Spearman correlations were carried out in order to assess the relationship between intervention scores (SPI-i component of the SPI) and physical activity scores.

Assessment of the study group (as a whole) revealed a significant inverse correlation between intervention scores and vigorous-intensity physical activity scores (r = -0.111, p = 0.05). Therefore, as the intervention scores increased, the scores for vigorous-intensity physical activity decreased.

This relationship was strengthened in females over the age of 65. This participant group displayed a significant negative correlation between intervention scores and vigorous-intensity physical activity scores (r = -0.398, p = 0.05). Therefore, as the intervention scores increased, the scores for vigorous-intensity physical activity decreased.

There were no significant correlations observed between intervention scores and physical activity scores in any of the other participant groups.

4.3.5.2 Modifying the SPI-i variable by eliminating disease duration from the overall score, revealed no significant relationships with physical activity scores

The analyses described in section 4.3.3.2 were repeated using the modified SPI-i variable. The purpose of the modification of this variable was to eliminate disease duration as a confounder and increase the weighting of previous interventions (see section 3.5.2 for more detail). Generally, the correlations observed in this analysis were weak. No significant correlations were observed between (modified) intervention scores and physical activity scores across any of the individual participant groups. These results suggest that disease duration, and perhaps age, may be important factors in activity engagement. Prior to modifying the SPI-i variable, a significant negative correlation between intervention scores and vigorous-intensity physical activity scores was observed in females over the age of 65 ($r = -0.398$, $p = 0.05$).

4.3.5.3 Further scrutinisation of the 'modified' SPI-i variable and physical activity scores show no significant results

The modified SPI-i variable was dichotomised and recoded as 0, indicating no previous interventions and 1, indicating at least 1 previous intervention (see section 3.5.4 for more detail). Mann-Whitney tests were then performed to detect any differences in physical activity scores for those who had received no interventions (0) and those who had received 1 or more (1). The results from this analysis revealed no significant differences in activity scores between the two groups.

4.3.5.4 Participants aged between 18 ad 65 years who failed to meet the AHA guidelines for physical activity, had significantly higher 'modified' SPI-i scores than those who did meet the guidelines

Finally, analyses were carried out using the modified SPI-i variable and the AHA data (as presented in section 4.6.2). Independent samples T tests were used to assess differences in SPI-i scores between those who did adhere to the AHA guidelines for physical activity and those who did not.

Assessment of the study group revealed that those who did not meet the AHA guidelines for physical activity had significantly higher (modified) SPI-i scores than those who did meet the guidelines (means: those who met the guidelines: 1.0, those who failed to meet the guidelines: 1.6; $t = -2.606$, $p = 0.01$,).

Similarly, in participants aged between 18 and 65 years, it was also found that those who did not meet the AHA guidelines for physical activity had significantly higher (modified) SPI-i scores than those who did meet the guidelines (means: those who met the guidelines: 1.01, those who failed to meet the guidelines: 1.6; $t = -2.471$, $p = 0.014$).

It was also observed that females who did not meet the AHA guidelines for physical activity had significantly higher (modified) SPI-i scores than those who did meet the guidelines (means: those who met the guidelines: 0.98, those who failed to meet the guidelines: 1.5; $t = -1.982$, $p = 0.05$).

There were no significant differences in the (modified) SPI-i scores between those who met the AHA guidelines for physical activity and those who did not, in any of the other participant groups.

4.3.5.5 The psychosocial impact of psoriasis, measured using the SPI-p, shows no correlation with physical activity scores

Spearman correlations were carried out in order to assess the relationship between the psychosocial impact of psoriasis (SPI-p component of the SPI) and physical activity scores. The SPI-p component of the SPI converts a 10 centimetre visual analogue psychosocial impact score to the nearest integer, ranging from 0 to 10 (Chularojanamontri et al., 2013).

There were no significant correlations observed between the psychosocial impact of psoriasis and physical activity in any of the individual participant groups.

4.3.5.6 The SPI-p scores did not vary significantly across the three levels of physical activity

The Kruskal Wallis test was used to detect whether there were any significant differences in SPI-p scores among the 3 categories of physical activity. For the purpose of this analysis, the categorical IPAQ score was used.

The results from this analysis indicated no significant difference in SPI-p scores across the 3 levels of physical activity in any of the participant groups.

4.3.5.7 The SPI-p scores did not vary significantly between those who met the AHA guidelines for physical activity and those who did not

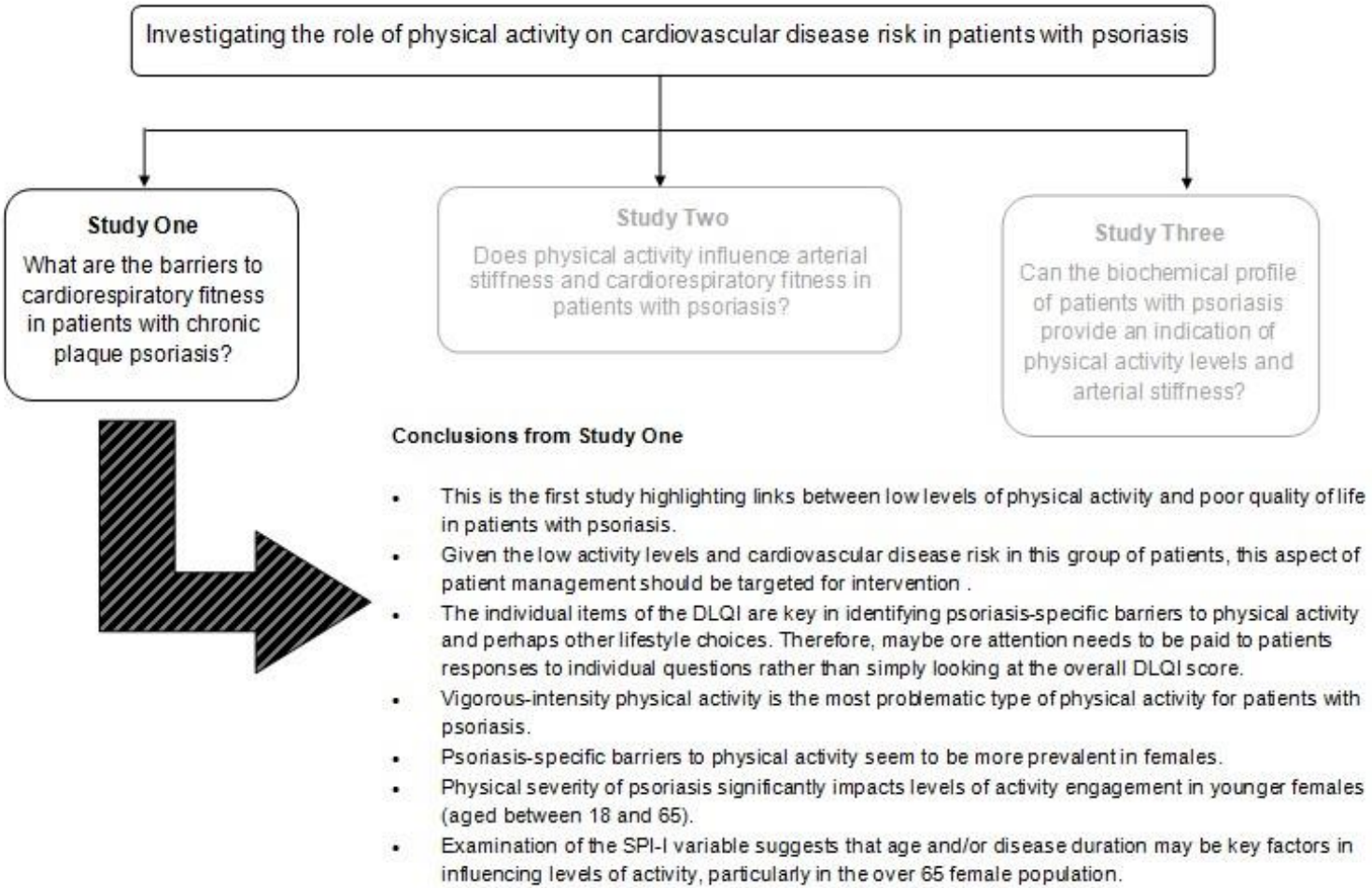
Finally, independent samples T tests were used to assess differences in SPI-p scores between those who met the AHA guidelines for physical activity and those who did not.

The results from these tests revealed no significant differences in SPI-p scores between those who met the guidelines for physical activity and those who did not.

4.3.6 Conclusions from study one

This is the first study highlighting links between low levels of physical activity and poor quality of life in patients with psoriasis. Given the low activity levels and cardiovascular disease risk in this group of patients, this aspect of patient management should be targeted for intervention. Additionally, the results from the current study show that the individual items of the DLQI are key in identifying psoriasis-specific barriers to physical activity and perhaps other lifestyle choices. Therefore, maybe more attention needs to be paid to patients' responses to individual questions rather than simply looking at the overall DLQI score. It is also evident from study one that vigorous-intensity physical activity is the most problematic type of physical activity for patients with psoriasis. Furthermore, psoriasis-specific barriers to physical activity seem to be more prevalent in females. The physical severity of psoriasis significantly impacts levels of activity engagement in younger females (aged between 18 and 65). Finally, the examination of the SPI-I variable suggests that age and/or disease duration may be key factors in influencing levels of activity, particularly in the over 65 female population (see figure 4.6.6 for a summary of the conclusions drawn from study one). It should also be considered that psoriatic arthritis may be impacting on activity levels in these patients. These aspects of the current study will be discussed in more detail in chapter seven.

Figure 4.6.6 Summary of the main conclusions drawn from study one of this PhD.



CHAPTER FIVE: IS THE INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE A RELIABLE INDICATOR OF ARTERIAL STIFFNESS AND CARDIORESPIRATORY FITNESS IN PATIENTS WITH PSORIASIS?

5.1 Hypothesis

Physical activity is important for cardiovascular health in patients with psoriasis and objective measurement of the amount of activity undertaken by patients with psoriasis has clinical utility.

5.2 Rationale

Previous studies have concluded that moderate to severe chronic plaque psoriasis may be independently associated with increased arterial stiffness (Gisondi et al., 2008b). Arterial stiffness, as measured by PWV, is a pre-clinical marker of atherosclerotic disease and subsequent CVD risk (Mackenzie et al., 2002). However, these studies fail to address the effects of lifestyle factors, particularly physical activity, on arterial stiffness in psoriasis patients.

Furthermore, there are currently no studies to date which have assessed the use of the DRA as an indicator of cardiorespiratory fitness. Previous studies have shown that aerobic physical activity significantly improved arterial stiffness and that the effect was enhanced with higher intensity aerobic activity (Ashor et al., 2014). Therefore, physical activity could be a key factor in helping to reduce the risk of atherosclerosis

and other cardiovascular events in patients with psoriasis. The present study examined the relationship between PWV, DRA and self-reported physical activity. The TensioMed arteriograph generates both the PWV value and the DRA simultaneously and so these data were collected as part of the same baseline dataset.

5.3 Results

5.3.1 Subject characteristics

Of the 242 subjects who took part, a median age of 49 was observed (IQR: 38-59) with 51.2% males and 48.8% females. All participants were identified as having chronic plaque psoriasis, 58.9% had a family history of the disease. The median PASI was 2.7 (IQR:0.9-6). Table 5.3.1 presents the characteristics of participants in this study. The median and IQR are presented for continuous variables and percentages are presented for categorical variables.

Table 5.3.1 Characteristics of study subjects.

	Study Group Two (n=242)	18-65's (n=209)	Over 65's (n=33)	All Males (n=124)	Males 18-65's (n=106)	Males over 65's (n=18)	All Females (n=118)	Females 18-65's (n=103)	Females over 65's (n=15)
Age	49 (38-59)	46 (37-53.5)	70 (67-73)	48 (39-58)	45 (37-52)	70 (67-74)	50 (38-60)	46 (36-54)	71 (67-73)
PASI	2.7 (0.9-6)	3 (1.1-6.6)	1.8 (0.3-3.3)	3.8 (1.6-8)	4 (2-8.5)	1.6 (0.2-4.3)	2.3 (0.6-4.4)	2.3 (0.6-4.9)	2.4 (0.3-2.8)
DLQI	4 (1-8)	4 (2-8)	3 (1-6)	4 (2-8)	4 (2-8.5)	2 (1-5)	4 (1-7)	4 (1-7)	6 (1-7)
Myocardial infarction (%)	3.7	2.9	9.1	4	2.8	11.1	3.4	2.9	6.7
Atrial fibrillation (%)	5.4	3.8	15.2	8.1	5.7	22.2	2.5	1.9	6.7
Angina (%)	4.5	2.4	18.2	5.6	4.7	11.1	3.4	0	26.7
Stroke (%)	0	0	0	0	0	0	0	0	0
Psoriatic arthritis (%)	22.9	24.2	15.2	23	26	5.6	22.9	22.3	26.7
Transient ischaemic attack (%)	0.8	0	6.1	0	0	0	1.7	0	13.3
Treatment for hypertension (%)	32.5	25.7	84.2	31.1	24.1	81.8	34.2	27.7	87.5
Total IPAQ score (MET-mins/week)	1957.5 (694.8-4135.5)	1980 (693-3999)	1786 (933-4625)	2217 (1002-4927)	2106 (742.5-4605.5)	4318 (1752-10638)	1691 (660-3132)	1782 (660-3304.5)	1065 (530.3-1859.6)
Walking score (MET-mins/week)	924 (330-2079)	792 (297-2079)	1188 (478.5-3811.5)	1188 (321.8-2772)	792 (297-2227.5)	1386 (684.8-4158)	792 (338-1782)	792 (280.5-1683)	1056 (412.5-2598.8)
Moderate-intensity activity score (MET-mins/week)	0 (0-720)	0 (0-720)	40 (0-2100)	170 (0-1200)	100 (0-960)	360 (0-3600)	0 (0-525)	0 (0-720)	0 (0-40)
Vigorous-intensity activity score (MET-mins/week)	0 (0-1200)	0 (0-1200)	0 (0-2160)	480 (0-1710)	320 (0-1440)	840 (0-4440)	0 (0-960)	0 (0-960)	0 (0-0)
Time spent sitting (minutes)	360 (240-480)	360 (240-480)	300 (180-360)	360 (300-480)	360 (300-502.5)	360 (240-360)	360 (240-480)	360 (240-480)	210 (120-360)
IPAQ category 1 (%)	23.4	23.6	22.2	17.3	18.6	7.7	29.6	28.7	35.7
IPAQ category 2 (%)	36.2	36.6	33.3	40	42.3	23.1	32.4	30.9	42.9
IPAQ category 3 (%)	40.4	39.8	44.4	42.7	39.2	69.2	38	40.4	21.4
AHA guidelines (% who adhere)	48.9	50.3	38.5	57.5	57	61.5	39.8	43.2	15.4
PWV (m/s)	8.2 (6.9-9.6)	7.8 (6.8-9.5)	9.5 (8.7-11.2)	7.9 (7-9.3)	7.7 (6.8-9)	9.5 (8.5-12.1)	8.3 (6.8-9.9)	8.2 (6.6-9.6)	9.6 (8.9-11.1)
DRA	46 (38.4-54.7)	47 (40-56.7)	36.8 (32.2-42.6)	46 (40-56)	47.7 (42-58)	38.8 (33.2-42.9)	45.2 (36.1-53.8)	47 (38.1-56)	32.7 (29.4-39.6)

5.3.2 PWV and DRA were significantly, negatively correlated in people with psoriasis

Correlation analyses were performed in order to assess the relationship between PWV and DRA.

Assessment of the study group identified a significant negative correlation between PWV and DRA was found ($r = -0.367$, $p = <0.01$). Therefore, as PWV values increased, the DRA values decreased.

Examination of age specific differences revealed a significant negative correlation between therse two variables in participants aged between 18 and 65 ($r = -0.325$, $p = <0.01$). This meant that as DRA values decreased, the PWV values increased. However, the correlation between PWV and DRA for participants over the age of 65 was not significant.

Examination of gender specific differences demonstrated that male participants had a significant negative correlation between PWV and DRA ($r = -0.237$, $p = 0.013$). Therefore, as PWV values increased, the DRA values decreased. However, when the male cohort was split into age bands (18-65 years and >65 years), no significant correlations were observed.

Upon examination of the female subjects a significant negative correlation between PWV and DRA was noted ($r = -0.435$, $p = <0.01$). A significant negative correlation was also observed in females aged 18-65 years ($r = -0.426$, $p = <0.01$). Therefore, as PWV values increased, the DRA values decreased. However, there was no significant correlation between PWV and DRA in females aged over 65 years.

Table 5.3.2 Summary of correlations between PWV and DRA (Spearman's Rho). Significant results are highlighted in bold font.

Group	Correlation coefficient (r value)	P value
Whole of study group 2	**-0.367**	**<0.01**
18-65 years	**-0.325**	**<0.01**
>65 years	0.13	0.484
All males	**-0.237**	**0.013**
Males 18-65 years	-0.151	0.15
Males >65 years	0.025	0.926
All females	**-0.435**	**<0.01**
Females 18-65 years	**-0.426**	**<0.01**
Females >65 years	0.275	0.342

5.3.3 PWV and vigorous-intensity physical activity scores were significantly, inversely correlated in males with psoriasis, aged 18-65

Assessment of the study group identified a significant negative correlation between PWV and vigorous-intensity physical activity ($r = -0.217$, $p = 0.002$). Therefore, as PWV values increased, scores for vigorous-intenisty activity decreased.

Examination of age specific differences revealed a significant negative correlation between PWV and vigorous-intensity physical activity in participants aged 18-65 years ($r = -0.265$, $p = <0.01$). Therefore, as PWV values increased, scores for vigorous-intenisty activity decreased. However, no significant correlations were observed in the over 65 age group.

Examination of gender specific differences showed no significant correlations between PWV and physical activity in male participants. However, when split according to age, males aged 18-65 years displayed a significant negative correlation between PWV and vigorous-intensity activity ($r = -0.286$, $p = 0.007$). Therefore, as PWV values increased, scores for vigorous-intenisty activity decreased. There were no significant correlations found in males over the age of 65.

Upon examination of the female participants, no significant correlations were observed between PWV and physical activity.

5.3.4 PWV values varied significantly between the high-levels of activity and the moderate-levels of activity groups in participants with psoriasis, aged 18- 65 years

The Kruskal-Wallis test was used to assess for any differences in PWV across the three categories of physical activity. Subjects were assigned to a category on the basis of the type and quantity of physical activity they took part in over the previous 7 days. The categories are numbered as 1, 2 and 3, representing low, moderate and high levels of physical activity, respectively. See table 3.1, section 3.5.2 for more detail on scoring of the IPAQ.

Assessment of the study group identified a significant difference in PWV values across the three categories of physical activity (mean ranks: low level of activity: 107.1, moderate level of activity: 108.4, high level of activity: 84.3; chi-square = 8.15, p = 0.017). Within each of these categories, there was a different proportion of patients, hence the variation in the mean ranks (as discussed in the methods chapter of this thesis, patients are assigned a category of activity upon calculation of their total IPAQ score, which varies between individuals). In order to determine which of the three groups were significantly different from one another, a post-hoc analysis was performed using the Dunn-Bonferroni test. The results from the post-hoc test revealed a significant difference in PWV values between the high-levels of activity and the moderate-levels of activity groups (adjusted p value = 0.028).

Examination of age specific differences highlighted a significant difference in PWV values across the three categories of activity in participants aged between 18 and 65

years (mean ranks: low level of activity: 93.4, moderate level of activity: 95.5, high level of activity: 71.5; chi-square = 9.05, p = 0.011). In order to determine which of the three groups were significantly different from one another, a post-hoc analysis was performed using the Dunn-Bonferroni test. The results from the post-hoc test revealed a significant difference in PWV values between the high-levels of activity and the moderate-levels of activity groups (adjusted p value = 0.017).

There were no significant correlations observed in the over 65 age group.

Examination of gender specific differences revealed no significant differences in PWV values across the three categories of physical activity.

5.3.5 PWV values did not vary significantly between those who adhered to the AHA guidelines for physical activity and those who did not

According to the AHA guidelines, in order to promote and maintain cardiorespiratory health, healthy adults should be achieving an energy expenditure of ≥500-1000 MET-minutes on a weekly basis. See section 3.5.4 for details on data coding. Independent samples t-tests were used to detect differences in PWV values between those who met the AHA guidelines for physical activity and those who did not.

It was observed that participants who did not adhere to the recommended guidelines for physical activity tended to have higher mean PWV values than those who met the guidelines. However, individual assessment of each participant group indicated no significant differences in PWV values between those who met the AHA guidelines for physical activity and those who did not.

5.3.6 PWV was not significantly correlated with sedentary behaviour in people with psoriasis

The final item on the IPAQ asks about how long an individual has spent sitting on a daily basis. This item is an additional indicator variable of sedentary behaviour and is not included as part of the overall IPAQ score. It was included in the analysis for this study in order to assess the relationship between PWV and sedentary behaviour. A positive correlation between PWV and time spent sitting was expected as arterial stiffness has previously been associated with physical inactivity (O'Donovan et al., 2014).

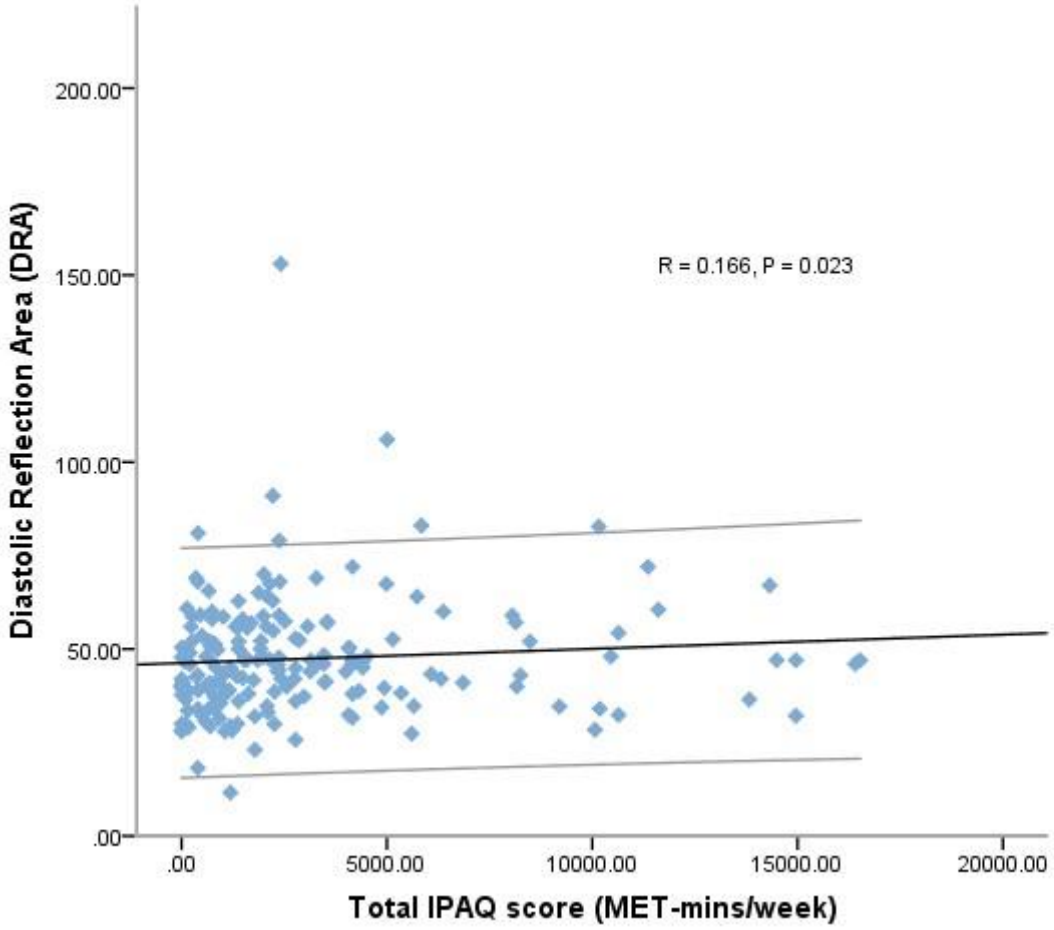
Assessment of each of the participant groups revealed no significant correlations between PWV and time spent sitting.

5.3.7 DRA and self-reported physical activity was significantly correlated in patients with psoriasis

As discussed in section 3.6.2, the DRA may be a novel indicator of cardiac fitness. The higher the DRA, the more optimal the filling condition of the left coronary artery during diastole and therefore, the greater the level of cardiac fitness.

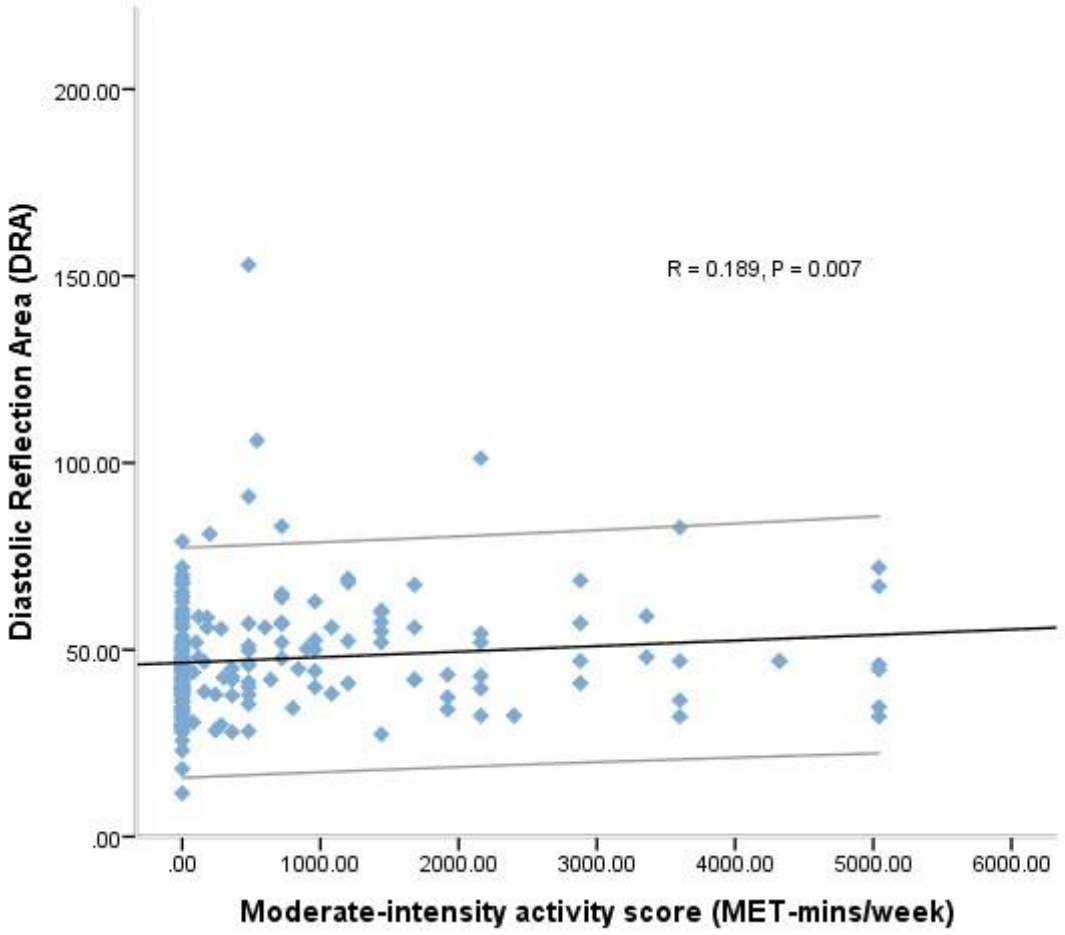
Assessment of the study group identified significant positive correlations between the following variables: DRA and total IPAQ score ($r = 0.166$, $p = 0.023$), DRA and moderate-intensity physical activity ($r = 0.189$, $p = 0.007$) and DRA and vigorous intensity physical activity ($r = 0.187$, $p = 0.006$).

Figure 5.3.7.1 Physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in patients with psoriasis (n=188)



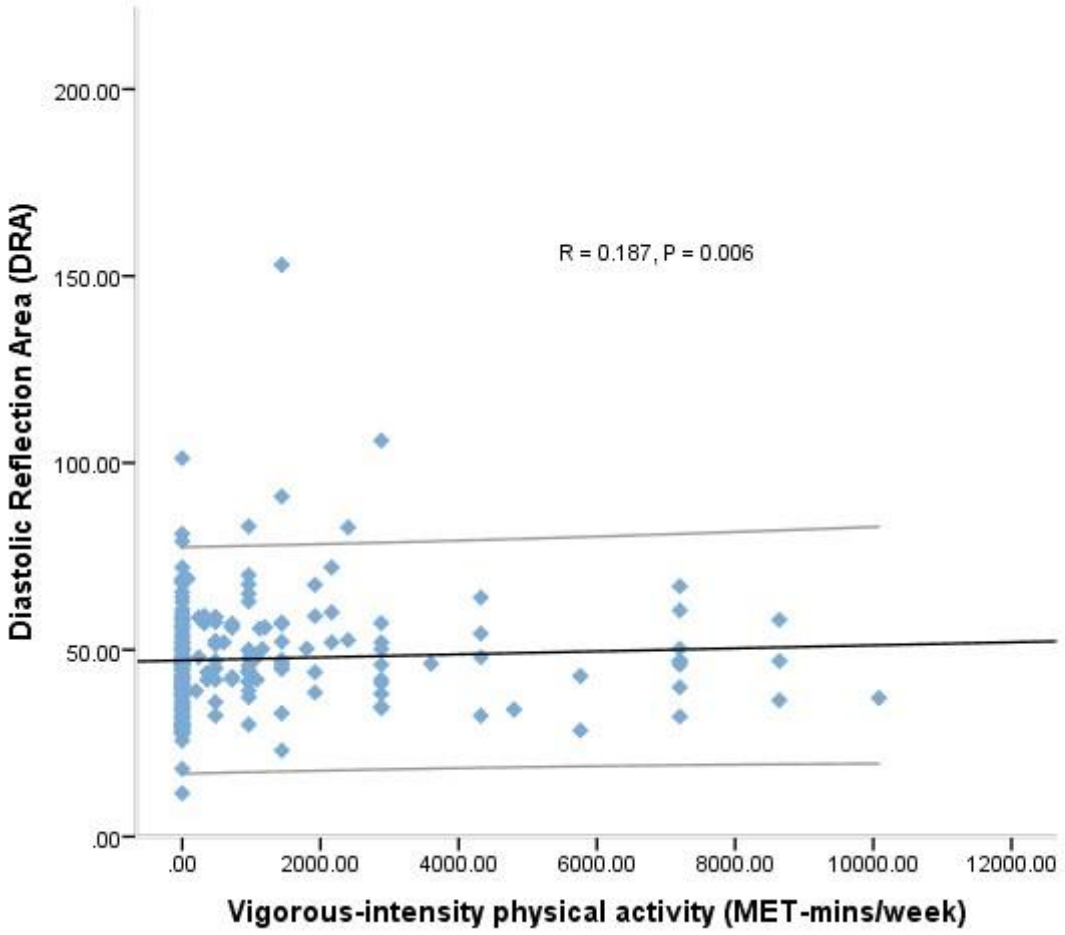
The scatter plot above depicts the correlation between DRA and physical activity for study group 2 as a whole. The significant positive correlation indicates that the higher the level of physical activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 22.3%; missing cases were excluded pairwise.

Figure 5.3.7.2 Moderate-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in patients with psoriasis (n=206)



The scatter plot above highlights the correlation between DRA and moderate-intensity physical activity for study group 2 as a whole. The significant positive correlation indicates that the higher the level of moderate-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. . Missing data: 14.9%; missing cases were excluded pairwise.

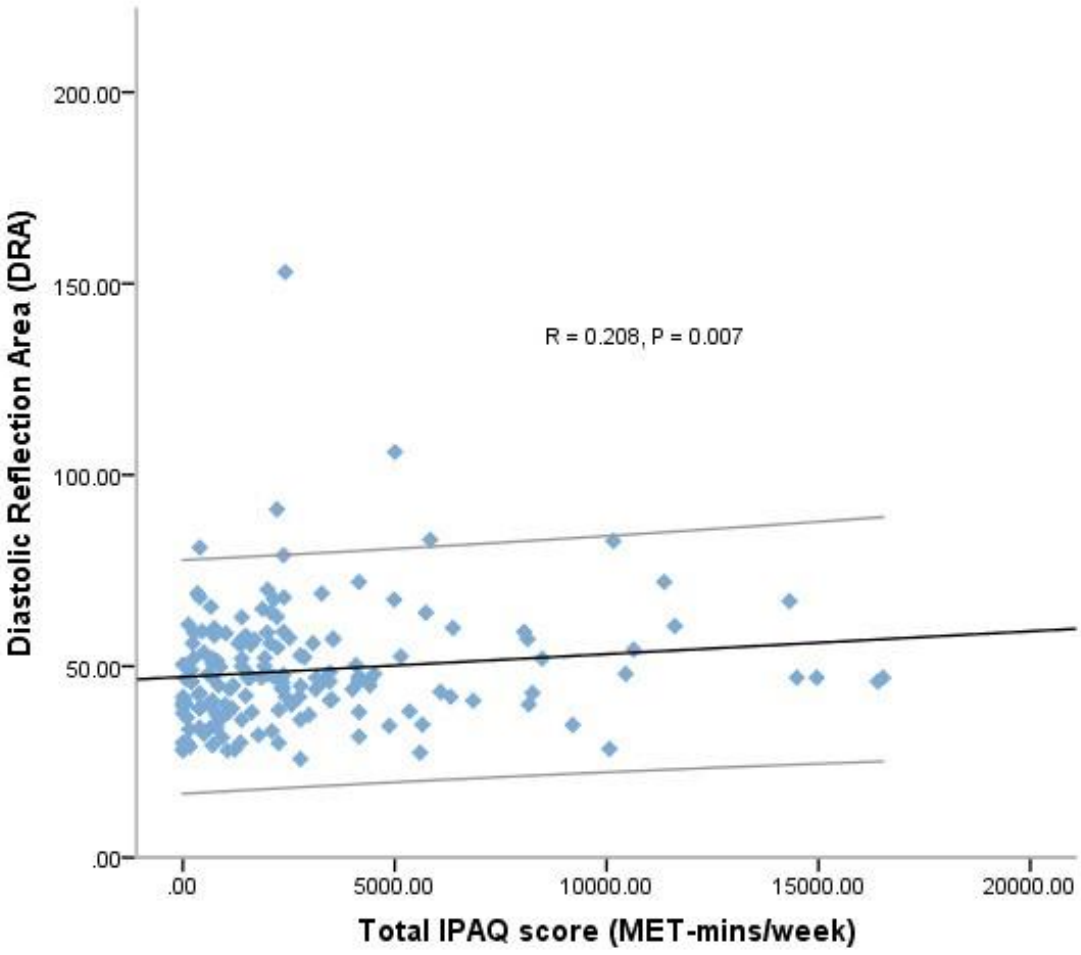
Figure 5.3.7.4 Vigorous-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in patients with psoriasis (n=214)



The scatter plot above illustrates the correlation between DRA and vigorous-intensity physical activity for study group 2 as a whole. The significant positive correlation indicates that the higher the level of vigorous-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. . Missing data: 11.6%; missing cases were excluded pairwise.

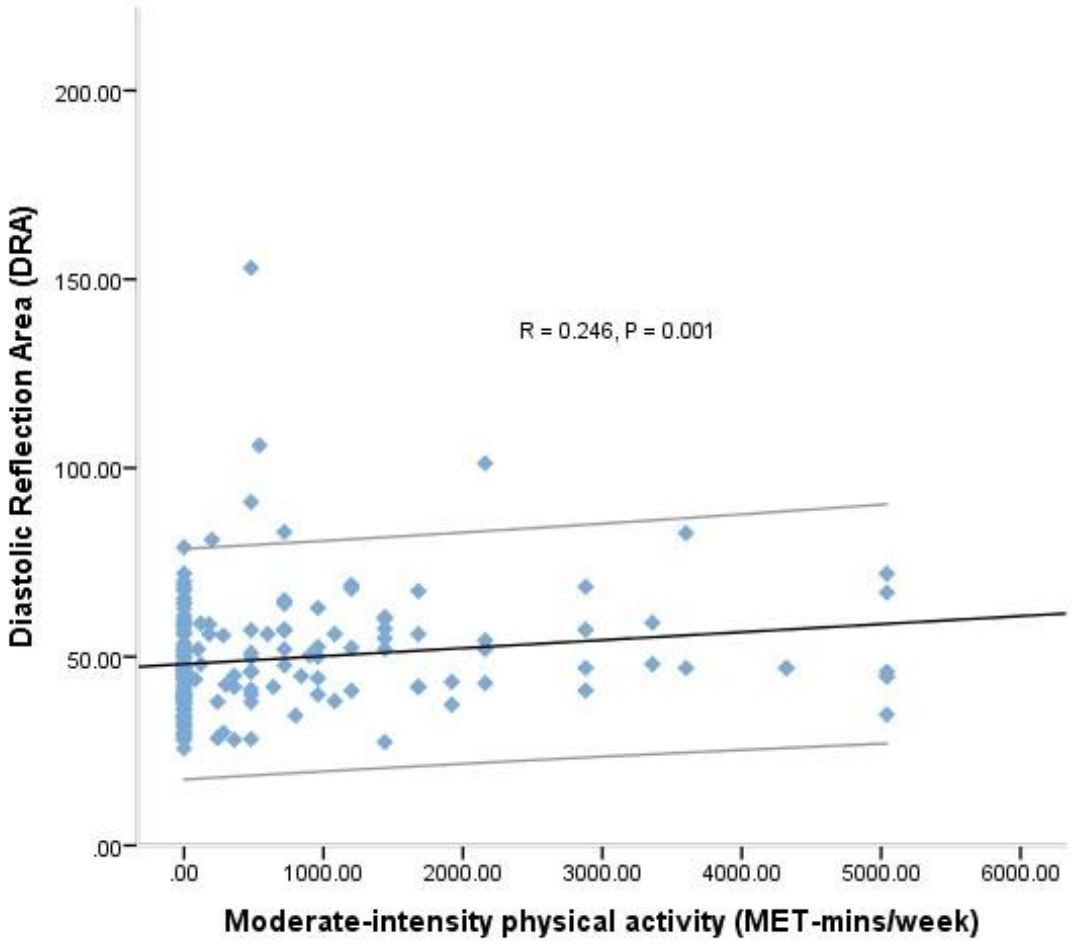
Examination of age specific differences revealed significant positive correlations in participants aged 18-65 years between the following variables: DRA and total IPAQ score ($r = 0.208$, $p = 0.007$), DRA and moderate-intensity physical activity ($r = 0.246$, $p = 0.001$) and DRA and vigorous intensity physical activity ($r = 0.202$, $p = 0.006$). However, no significant correlations were observed in the over 65 age category.

Figure 5.3.7.5 Physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in patients with psoriasis aged between 18 and 65 years (n=167)



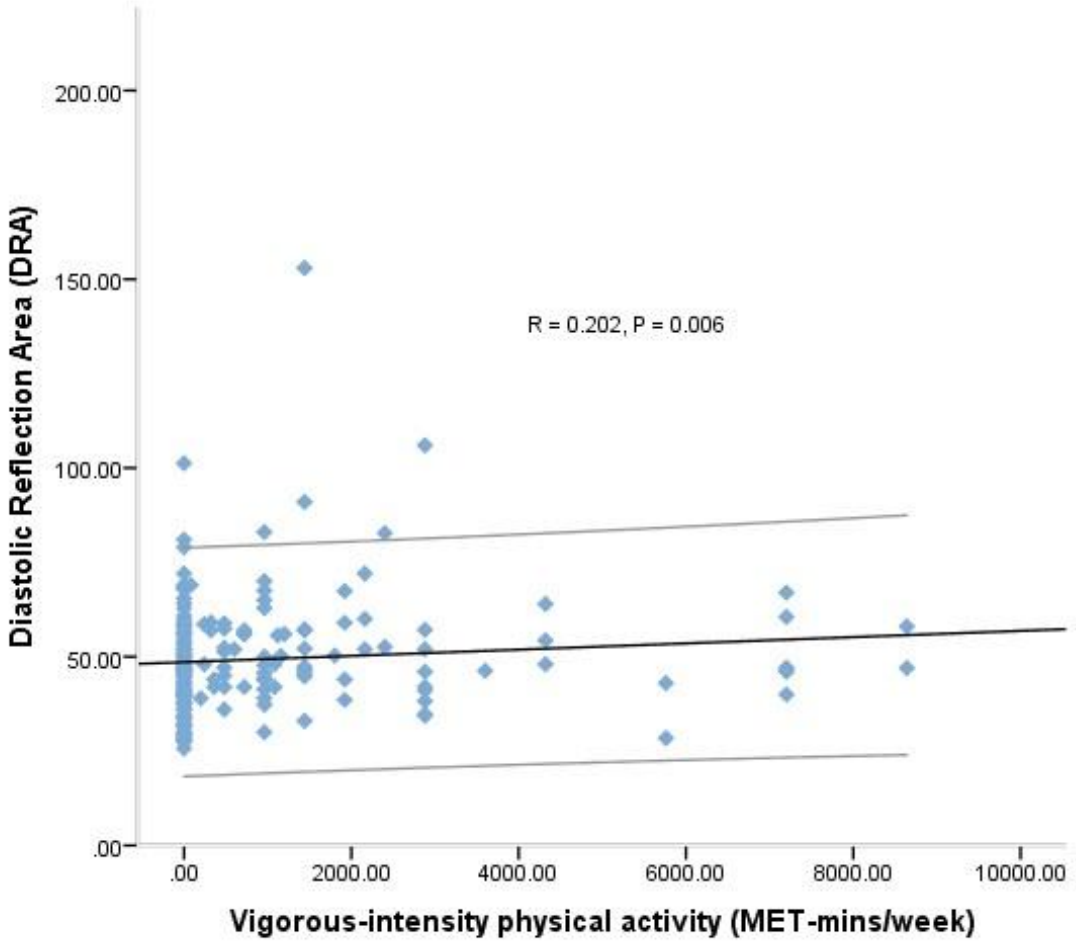
The scatter plot above depicts the correlation between DRA and physical activity for participants aged between 18 and 65. The significant positive correlation indicates that the higher the level of physical activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. . Missing data: 20.1%; missing cases were excluded pairwise.

Figure 5.3.7.6 Moderate-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in patients with psoriasis aged between 18 and 65 years (n=179)



The scatter plot above illustrates the correlation between DRA and moderate-intensity physical activity for participants aged between 18 and 65. The significant positive correlation indicates that the higher the level of moderate-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 14.4%; missing cases were excluded pairwise.

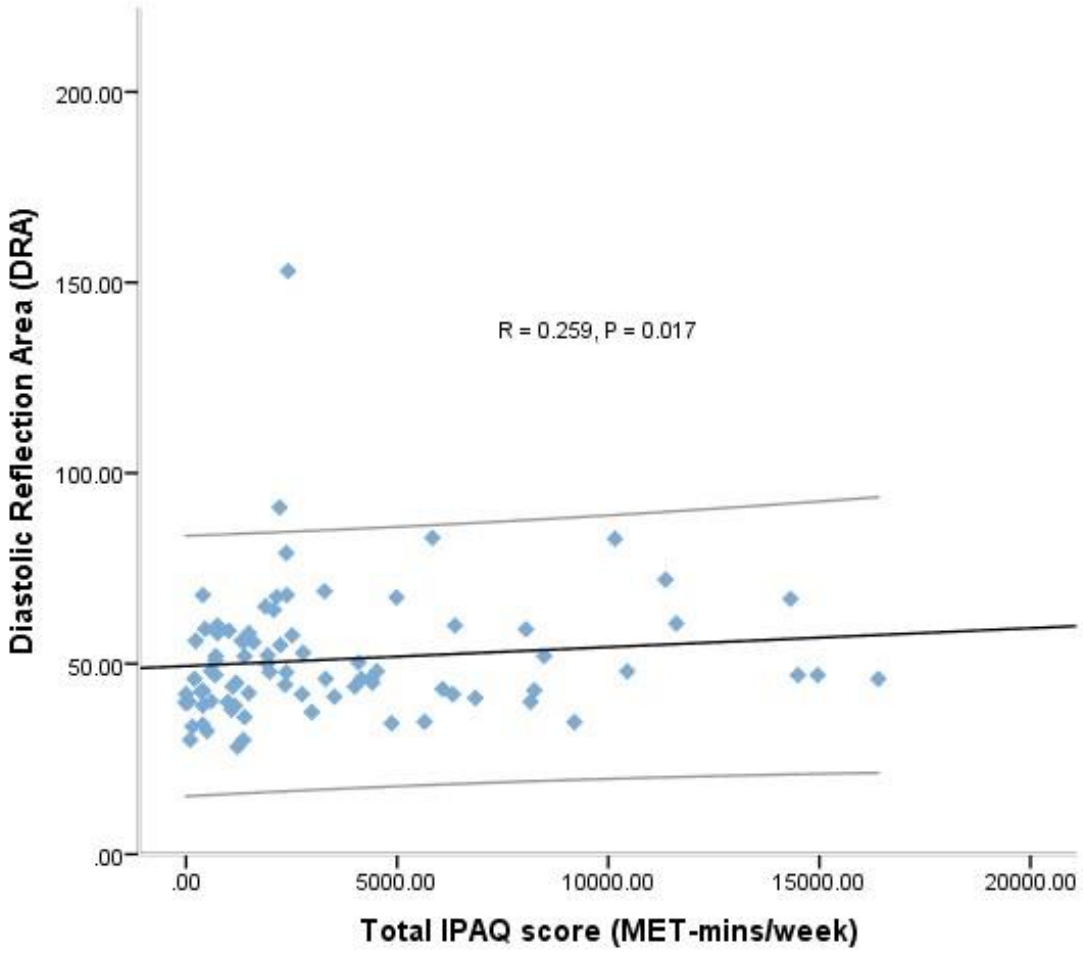
Figure 5.3.7.7 Vigorous-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in patients with psoriasis aged between 18 and 65 years (n=185)



The scatter plot above highlights the correlation between DRA and vigorous-intensity physical activity for participants aged between 18 and 65. The significant positive correlation indicates that the higher the level of vigorous-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 11.5%; missing cases were excluded pairwise.

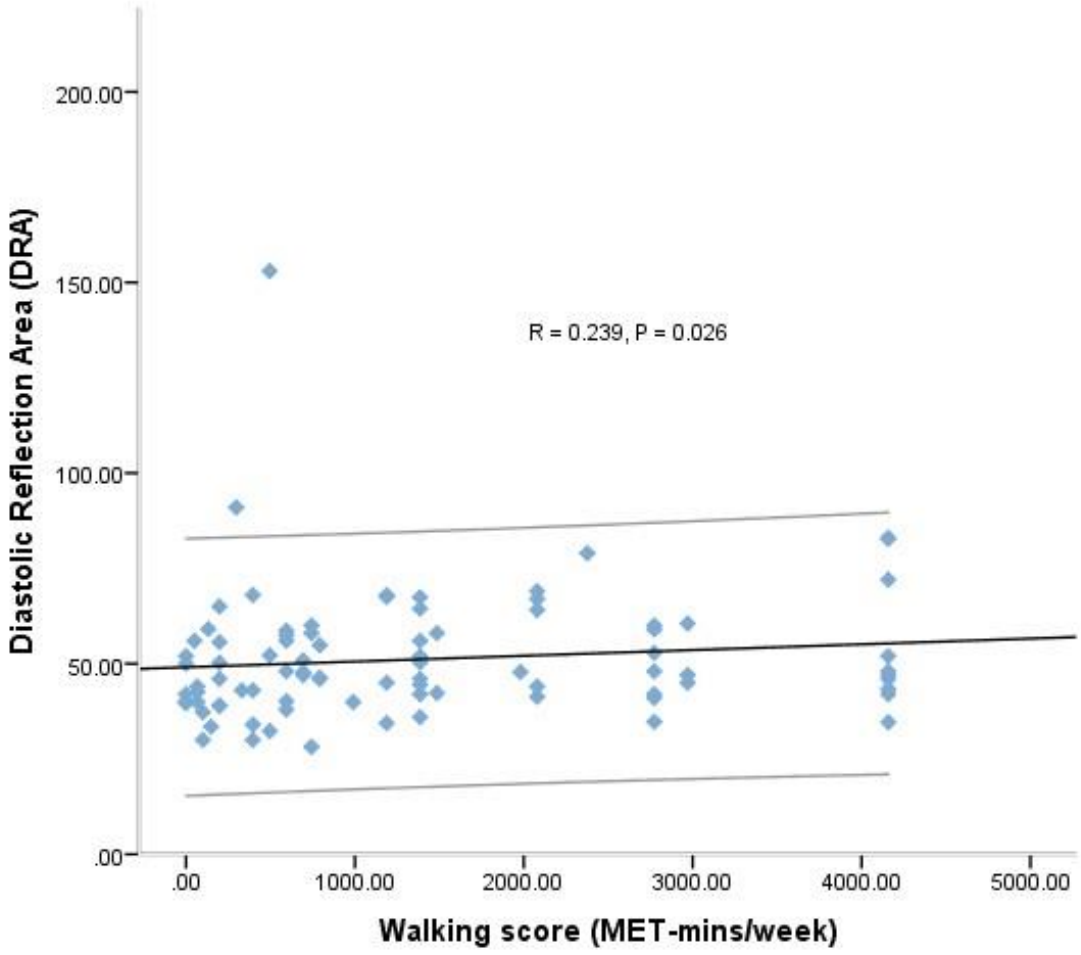
Examination of gender specific differences revealed no significant correlations between self-reported physical activity and DRA in males. However, when split into the different age bands various significant results were obtained. Males, aged between 18 and 65 years, had significant positive correlations between: DRA and total IPAQ scores ($r = 0.259$, $p = 0.017$), DRA and walking scores ($r = 0.239$, $p = 0.026$) and DRA and moderate-intensity physical activity ($r = 0.228$, $p = 0.03$).

Figure 5.3.7.8 Physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in males with psoriasis aged between 18 and 65 years (n=84)



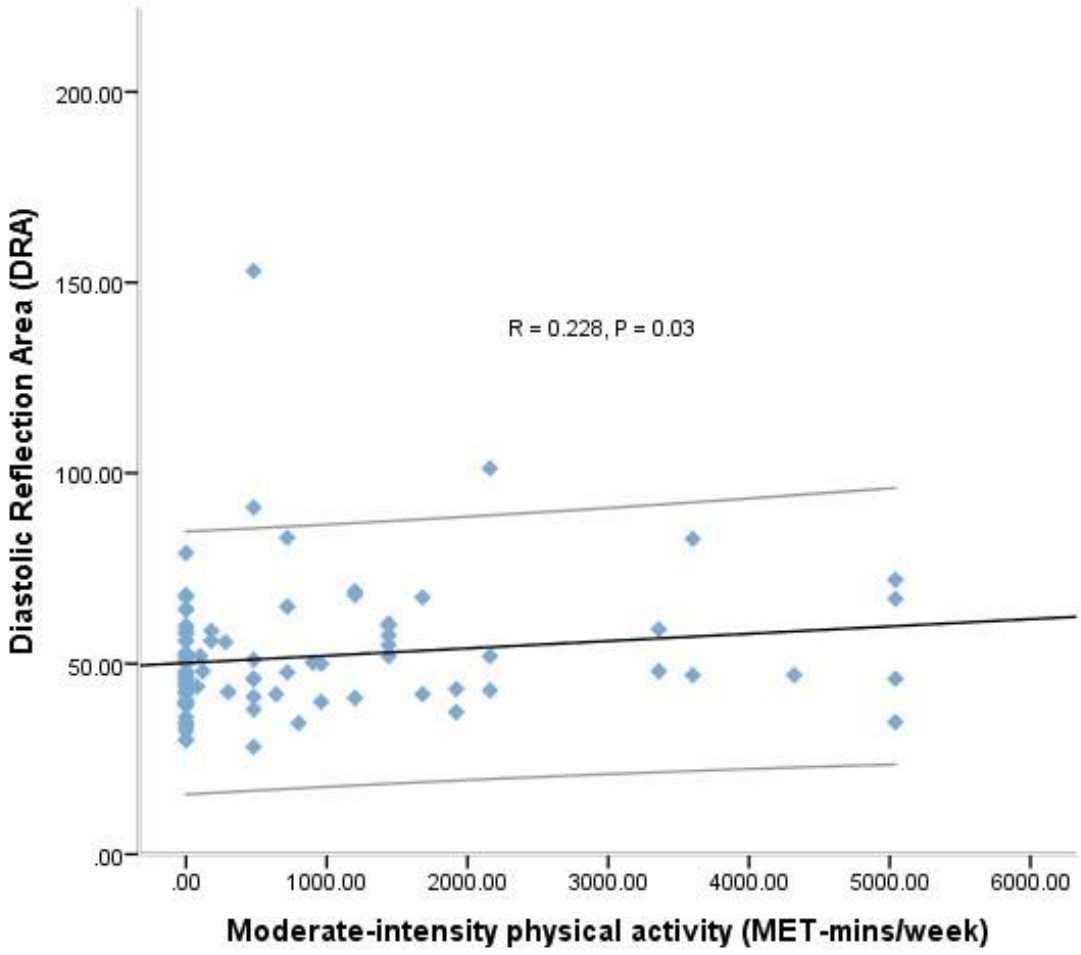
The scatter plot above shows the correlation between DRA and physical activity for male participants aged between 18 and 65. The significant positive correlation indicates that the higher the level of physical activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 20.8%; missing cases were excluded pairwise.

Figure 5.3.7.9 Walking was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in males with psoriasis aged between 18 and 65 years (n=87)



The scatter plot above illustrates the correlation between DRA and mild-intensity physical activity (walking) for male participants aged between 18 and 65. The significant positive correlation indicates that the higher the level of mild-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 17.9%; missing cases were excluded pairwise.

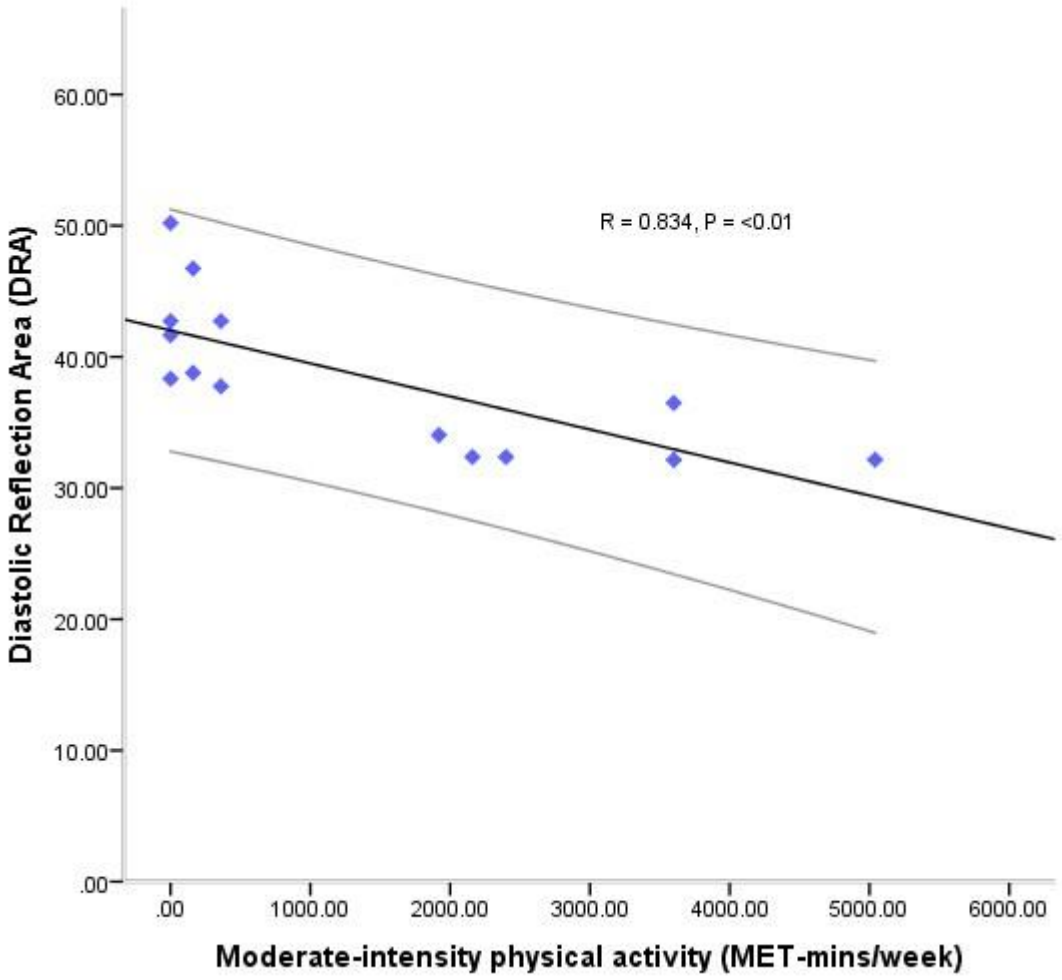
Figure 5.3.7.10 Moderate-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in males with psoriasis aged between 18 and 65 years (n=90)



The scatter plot above illustrates the correlation between DRA and moderate-intensity physical activity for male participants aged between 18 and 65. The significant correlation indicates that the higher the level of moderate-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 17.9%; missing cases were excluded pairwise.

Males over the age of 65 displayed a significant negative correlation between DRA and moderate-intensity physical activity ($r = 0.834$, $p = <0.01$).

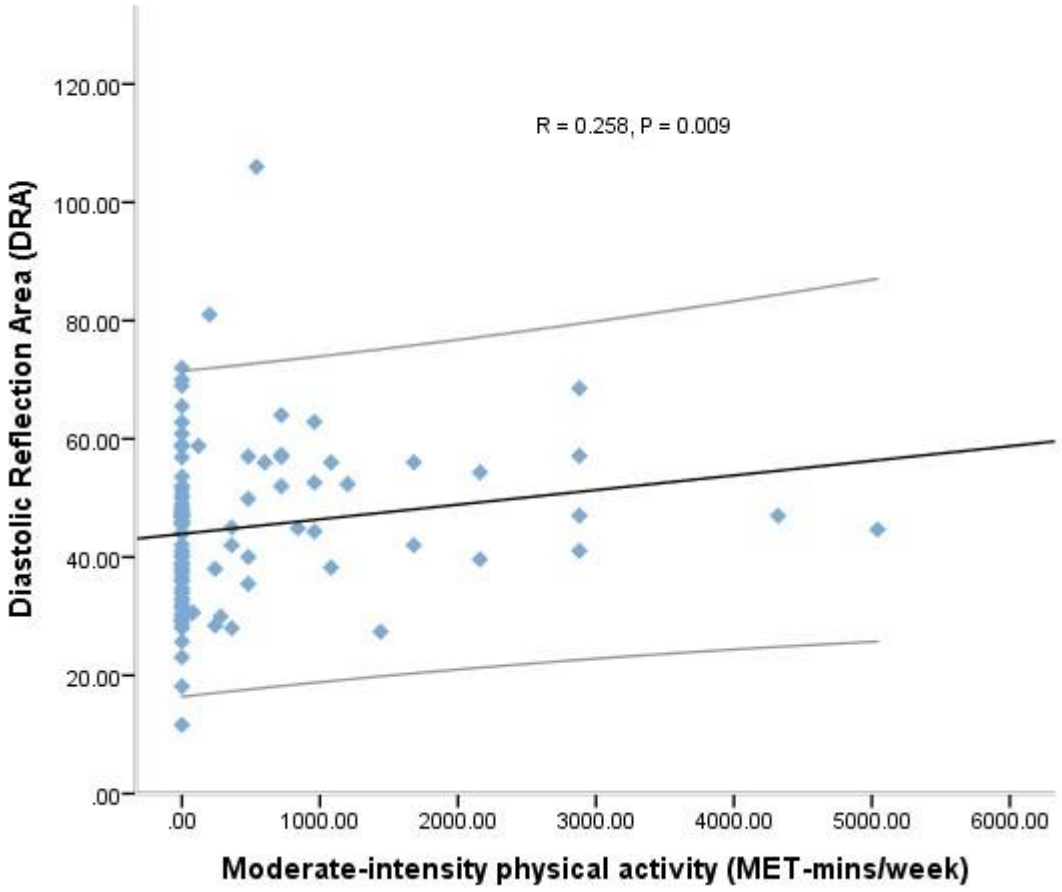
Figure 5.3.7.11 Moderate-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in males with psoriasis over the age of 65 (n=27)



The scatter plot above illustrates the correlation between DRA and moderate-intensity physical activity for male participants over the age of 65. The significant correlation indicates that the higher the level of moderate-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 18.2%; missing cases were excluded pairwise.

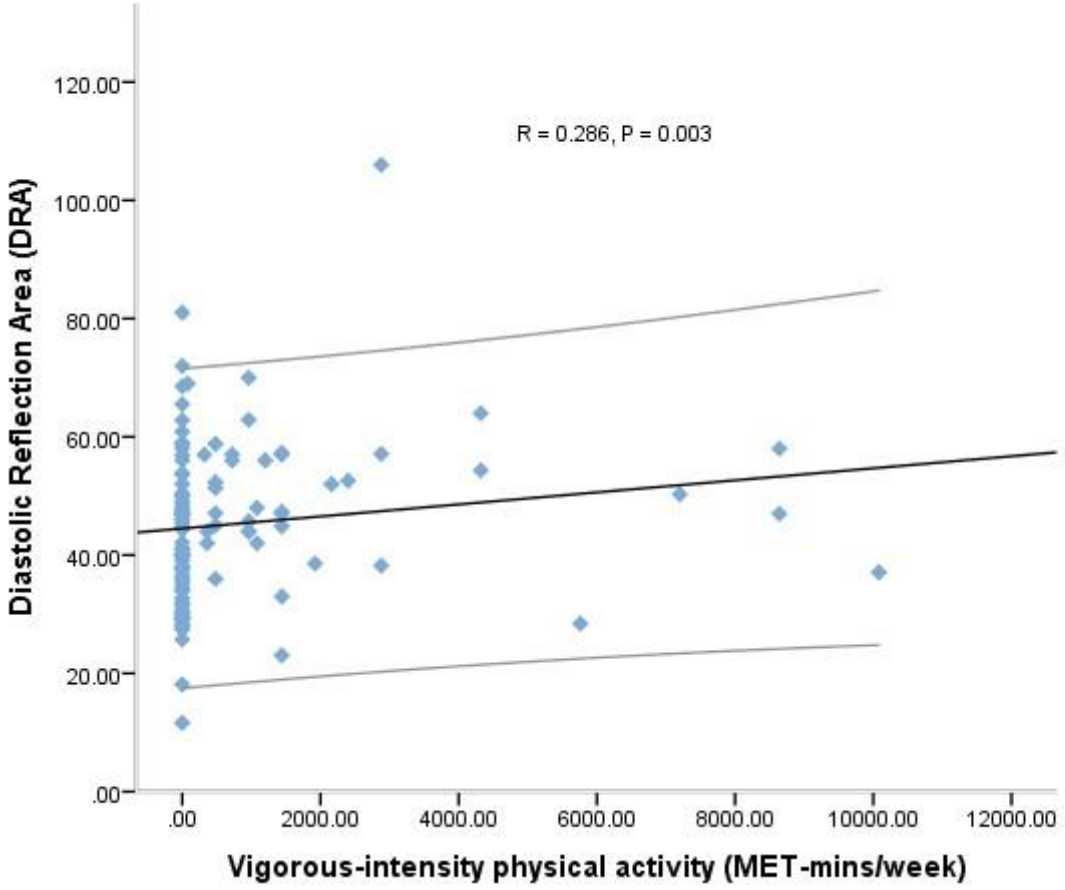
Upon examination of all female participants, significant positive correlations were indicated between DRA and moderate-intensity activity ($r = 0.258$, $p = 0.009$) and DRA and vigorous-intensity activity ($r = 0.286$, $p = 0.003$).

Figure 5.3.7.12 Moderate-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in females with psoriasis (n=102)



The scatter plot above highlights the correlation between DRA and moderate-intensity physical activity for female participants. The significant positive correlation indicates that the higher the level of moderate-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 13.6%; missing cases were excluded pairwise.

Figure 5.3.7.13 Vigorous-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in females with psoriasis (n=109)

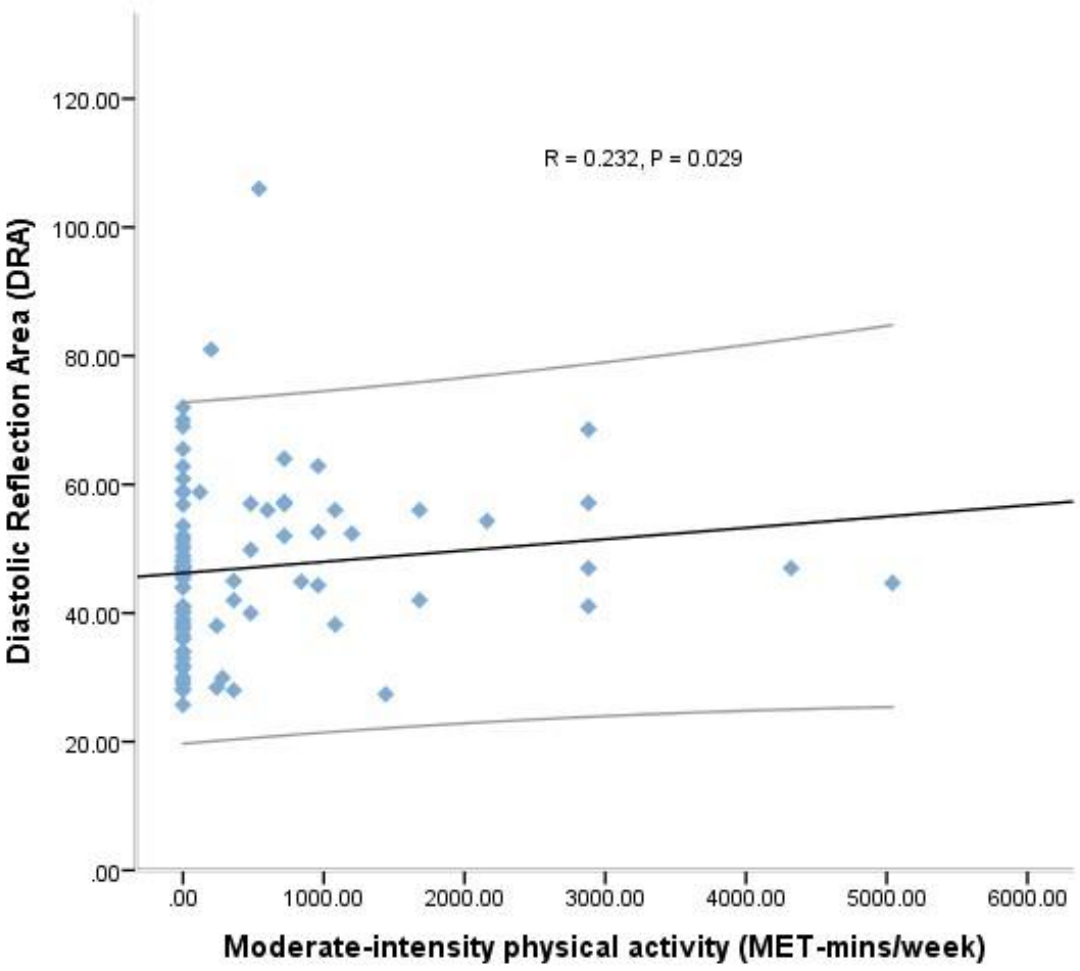


The scatter plot above shows the correlation between DRA and vigorous-intensity physical activity for female participants. The significant positive correlation indicates that the higher the level of vigorous-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 7.6%; missing cases were excluded pairwise.

Females aged between 18 and 65 also showed significant positive correlations between DRA and moderate-intensity activity (r = 0.232, p = 0.029) and DRA and

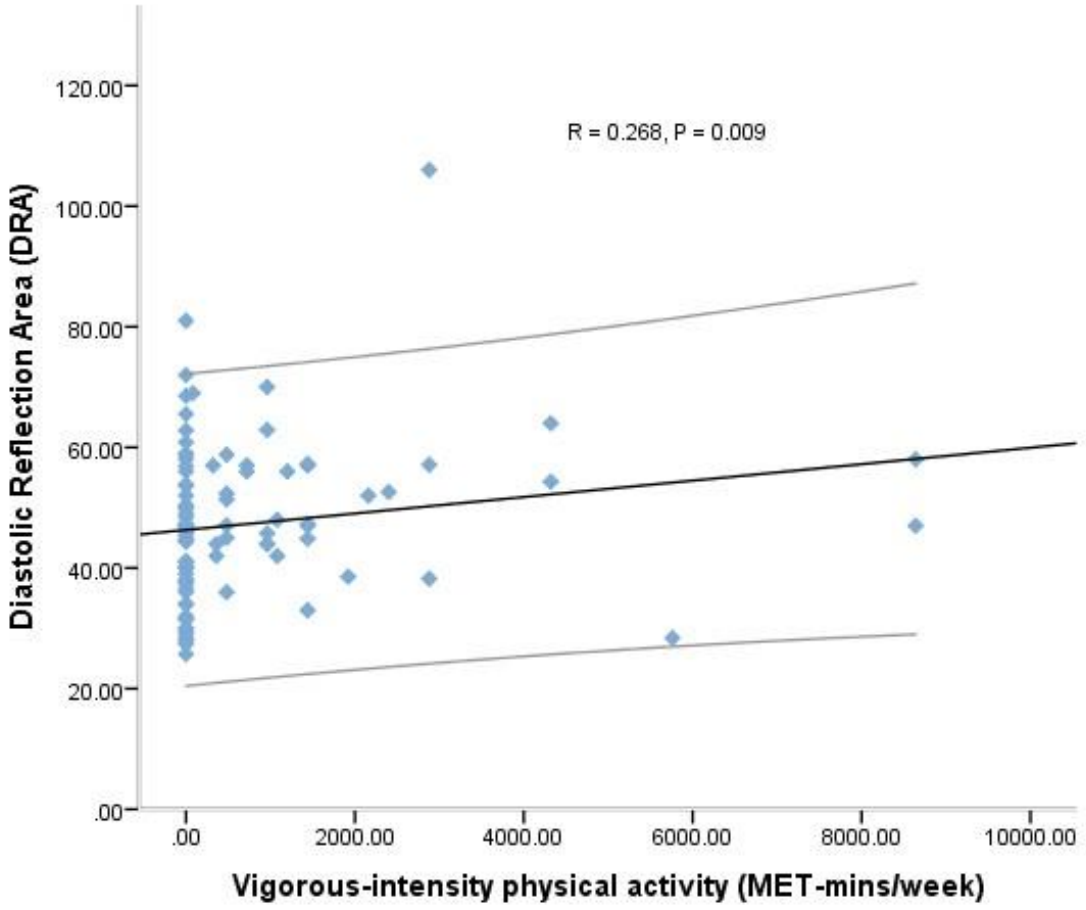
vigorous-intensity activity ($r = 0.268$, $p = 0.009$). There were no significant correlations in females over the age of 65.

Figure 5.3.7.14 Moderate-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in females with psoriasis aged between 18 and 65 years (n=89)



The scatter plot above depicts the correlation between DRA and moderate-intensity physical activity for female participants aged between 18 and 65. The significant positive correlation indicates that the higher the level of moderate-intensity activity, the greater the DRA value is. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals.n Missing data: 13.6%; missing cases were excluded pairwise.

Figure 5.3.7.15 Vigorous-intensity physical activity was significantly correlated with diastolic reflection area, a clinical measure of current cardiorespiratory fitness, in females with psoriasis aged between 18 and 65 years (n=94)



The scatter plot above illustrates the correlation between DRA and vigorous-intensity physical activity for female participants aged between 18 and 65. The significant positive correlation indicates that the higher the level of vigorous-intensity activity, the greater the DRA value is. It is important to note the clustering of participants at 0 MET-mins/week of vigorous-intensity physical activity. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 8.7%; missing cases were excluded pairwise.

5.3.8 DRA values varied significantly between the low-levels of activity and the high-levels of activity groups in participants with psoriasis, aged 18-65 years

The Kruskal-Wallis test was used to assess for differences in DRA across the three categories of physical activity.

Assessment of study group two as a whole revealed a significant difference in DRA values across the three categories of physical activity ($p = 0.047$, chi-square = 6.12). In order to determine which categories of activity presented significant differences in DRA, a post-hoc analysis was performed using the Dunn-Bonferroni test. The results from the post-hoc test revealed a significant difference in DRA values between the low-levels of activity and the high-levels of activity groups (adjusted p value = 0.047).

Examination of age specific differences highlighted a significant difference in DRA values across the three categories of activity in participants aged between 18 and 65 years (mean ranks: low level of activity: 70.4, moderate level of activity: 92.8, high level of activity: 94.6; chi-square = 6.9, $p = 0.032$). In order to determine which categories of activity presented significant differences in DRA, a post-hoc analysis was performed using the Dunn-Bonferroni test. The results from the post-hoc test revealed a significant difference in DRA values between the low-levels of activity and the high-levels of activity groups (adjusted p value = 0.042).

In participants over the age of 65, there was no significant difference in DRA values, across the three categories of activity.

Examination of gender specific differences revealed no significant difference in DRA values across the three categories of activity in the male cohort as a whole or the male subgroups (18-65's and over 65's).

Additionally, there were no significant differences detected in the female cohort as a whole or the female subgroups (18-65's and over 65's).

5.3.9 DRA values were significantly lower in people with psoriasis, aged 18-65 years, who failed to meet the AHA guidelines for physical activity

Independent samples t-tests were used to detect differences in DRA values between those who met the AHA guidelines for physical activity and those who did not. It was observed that participants who did not adhere to the recommended guidelines for physical activity tended to have lower mean DRA values than those who met the guidelines.

Assessment of the study group identified a significant difference in DRA values between those who met the AHA guidelines for physical activity and those who did not (mean DRA's: those who met the guidelines for physical activity: 51.6, those who did not meet the guidelines: 43.8; $t = 3.68$, $p<0.001$).

Examination of age specific differences indicated a significant difference between the two groups in participants aged between 18 and 65 years (mean DRA's: those who met the guidelines for physical activity: 53.4, those who did not meet the guidelines: 45.5; $t = 3.47$, $p = 0.001$). However, there was no significant difference between those who met the AHA guidelines and those who did not, in participants over the age of 65.

Examination of gender specific differences revealed a significant difference in males who met the AHA guidelines for physical activity and those who did not (mean DRA's: those who met the guidelines for physical activity: 52.7, those who did not meet the guidelines: 46.5; $t = 2.0$, $p = 0.048$).

When split into the difference age bands, a significant difference was noted in males aged between 18 and 65 years (mean DRA's: those who met the guidelines for physical activity: 55.1, those who did not meet the guidelines: 47.2; $t = 2.31$, $p = 0.023$). However, there was no significant difference detected in males over the age of 65.

Similarly a significant difference in DRA values was observed in females who met the AHA guidelines for physical activity and those who failed to meet the guidelines (mean DRA's: those who met the guidelines for physical activity: 50.1, those who did not meet the guidelines: 41.9; $t = 2.98$, $p = 0.004$).

When split into the difference age bands, a significant difference was noted in females aged between 18 and 65 years (mean DRA's: those who met the guidelines for physical activity: 51.1, those who did not meet the guidelines: 44.2; $t = 2.47$, $p = 0.015$). However, there was no significant difference detected in females over the age of 65.

5.3.10 DRA is significantly, inversely correlated with sedentary behaviour in females with psoriasis, aged 18-65

The 'sitting' variable included in the IPAQ assessment is an indicator of sedentary behaviour. A significant negative correlation was anticipated between DRA and time spent sitting given the postulate that the more inactive a person is, the lower the DRA value is expected to be.

Assessment of the study group revealed no significant correlation between DRA and time spent sitting.

Examination of age specific differences highlighted a significant negative correlation between the DRA and time spent sitting ($r = -0.166$, $p = 0.036$). Therefore, the longer the sitting time was, the lower the DRA value.

However, there was no significant correlation between the two variables in participants over the age of 65.

Examination of gender specific differences revealed no significant correlations in the male participants.

Upon examination of the female participants there was no significant correlation between the DRA and time spent sitting. However, when split into the different age bands a significant negative correlation between DRA and time spent sitting was observed in females aged between 18 and 65 years ($r = -0.242$, $p = 0.036$). Therefore, the longer the sitting time was, the lower the DRA value.

5.4 Hierarchical regression models

This section will present the results obtained from hierarchical regression analyses. Two hierarchical regression models were constructed for PWV and DRA, respectively, with each of these variables as the dependent variable.

Sensitivity analyses were carried out in order in order to assess the impact of outliers on the regression models presented in this section. The results of these analyses revealed that the absence of outliers did not improve the overall model fit or the beta coefficients. Therefore a decision was made to keep the outlying data points in the models.

5.4.1 Age, smoking and treatment for hypertension were found to be significant predictors of PWV in patients with psoriasis

The purpose of constructing this model was to see whether self-report physical activity was a significant predictor of PWV whilst controlling for various confounding factors, including age (entered as a continuous variable), smoking status, alcohol consumption and treatment for hypertension (all entered as categorical variables). The alcohol variable was originally recorded as units per week, however it was recoded into a categorical variable (0 and 1) which recognises individuals who consume more than the recommended units of alcohol per week. According to the NHS guidelines both males and females should not consume more than 14 units of alcohol a week. Therefore, for the purpose of recoding this variable, 0 indicated that participants consume ≤14 units and 1 indicated that participants consume 15 or more units on average each week. BMI was excluded from the model as it showed no significant relationship with PWV in a correlation analysis ($r=0.326$, $p=0.31$).

Since vigorous-intensity activity scores generated the most significant correlations with PWV (see section 5.6.3), this parameter was selected as the activity variable for the regression model.

In summary, the independent variables which were entered into this model included age, smoking status, treatment for hypertension, alcohol consumption and vigorous-intensity physical activity scores. The independent variables were entered in this sequence in order to determine whether levels of vigorous-intensity physical activity, in which people engage in, is a significant predictor of their PWV when statistically controlling for the other independent variables.

Therefore, a three stage hierarchical multiple regression was conducted with PWV as the dependent variable. Initially, PWV was transformed using the logarithm function in order to make it more ‘normally’ distributed, however, this did not affect the

independent variables in the model and it did not improve the overall model fit. Age was entered into the first block of the regression in order to control for the influence of this demographic variable. The smoking, hypertension and alcohol variables were entered into block two of the model and the vigorous-intensity physical activity variable was entered into block three. The results from this multiple regression analysis are presented in table 5.6.5.1.

Table 5.4.1 Summary of hierarchical regression analysis for variables predicting PWV values (n=219)

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.299**	**<0.001**	**0.299**	**<0.001**
Age	**0.546**	**<0.001**				
Block 2:			**0.376**	**<0.001**	**0.077**	**0.001**
Age	**0.407**	**<0.001**				
Smoking	**0.171**	**0.014**				
Treatment for hypertension	**0.276**	**0.001**				
Alcohol	-0.042	0.543				
			0.377	**<0.001**	0.001	0.677
Block 3:	**0.414**	**<0.001**				
Age	**0.171**	**0.014**				
Smoking	**0.266**	**0.003**				
Treatment for hypertension	-0.043	0.532				
Alcohol	-0.03	0.677				
Vigorous-intensity physical activity						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: PWV. Statistically significant values are highlighted in bold. Missing data: 9.5%.

Block 1 of the hierarchical regression revealed that age accounted for 29.9% of the variation in PWV values. The R^2 change for block one 1 of this model was significant ($p < 0.001$). Introducing smoking, treatment for hypertension and alcohol in block 2 of this model explained an additional 7.7%. This change in R^2 was also significant ($p = 0.001$). Adding the vigorous-intensity physical activity variable in block 3 explained a further 0.1% of the variation in PWV values, however, the change in R^2 was not significant. Together the five variables accounted for 37.7% of the variance in PWV values. This model as a whole was significant ($F = 16.3$, $p = <0.001$). The variables which made a significant contribution to the regression model, in order of importance, include: age ($\beta = 0.414$, $p = <0.001$), smoking ($\beta = 0.171$, $p = 0.014$) and treatment for hypertension ($\beta = 0.266$, $p = 0.003$).

5.4.2 Age was found to be a significant predictor of DRA in patients with psoriasis

The purpose of constructing this model was to see whether self-report physical activity was a significant predictor of DRA, (an objective measure of cardiorespiratory fitness) whilst controlling for various confounding factors. Therefore, the aim of this model was to see whether the IPAQ questionnaire is appropriate to use in the clinic as a measure of activity.

The independent variables which were entered into this model included: age, sex, smoking status, history of myocardial infarction, history of angina and total IPAQ scores. The 'total IPAQ score' variable was chosen for this regression model as it showed the most significant correlations with DRA.

Therefore, a three stage hierarchical multiple regression was conducted with DRA as the dependent variable. Initially, DRA was transformed using the logarithm function in order to make it more 'normally' distributed, however, this did not affect the independent variables in the model and it did not improve the overall model fit. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. The smoking, history of myocardial infarction and history of angina variables were entered into block two of the model and the total IPAQ score variable was entered into block three. The results from this multiple regression analysis are presented in table 5.6.5.2.

Table 5.4.2 Summary of hierarchical regression analysis for variables predicting DRA values (n=224).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.308**	**<0.001**	**0.308**	**<0.001**
Age	**-0.539**	**<0.001**				
Sex	**-0.136**	**0.046**				
			0.313	**<0.001**	0.004	0.813
Block 2:	**-0.561**	**<0.001**				
Age	-0.134	0.052				
Sex	-0.012	0.867				
Smoking	0.049	0.513				
History of MI	0.033	0.665				
History of angina			**0.317**	**<0.001**	0.005	0.306
	-0.564	**<0.001**				
Block 3:	-0.12	0.088				
Age	-0.02	0.778				
Sex	0.052	0.485				
Smoking	0.04	0.598				
History of MI	0.073	0.306				
History of angina						
Total IPAQ score						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: DRA. Statistically significant values are highlighted in bold. Missing data: 7.4%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 30.8% of the variation in DRA values. The R^2 change for block one 1 of this model was significant ($p < 0.001$). Introducing smoking, history of myocardial infarction and history of angina in block 2 of this model explained an additional 0.4%, however this change in R^2 was not significant. Adding the total IPAQ score variable in block 3 explained a further 0.5% of the variation in DRA values, however, the change in R^2 was also not significant. Together the six variables accounted for 31.7% of the variance in DRA values. This model as a whole was significant ($F = 11.3$, $p = <0.001$). The only variable which made a significant contribution to the regression model was age ($\beta = -0.564$, $p = <0.001$).

5.5 Conclusions from study two

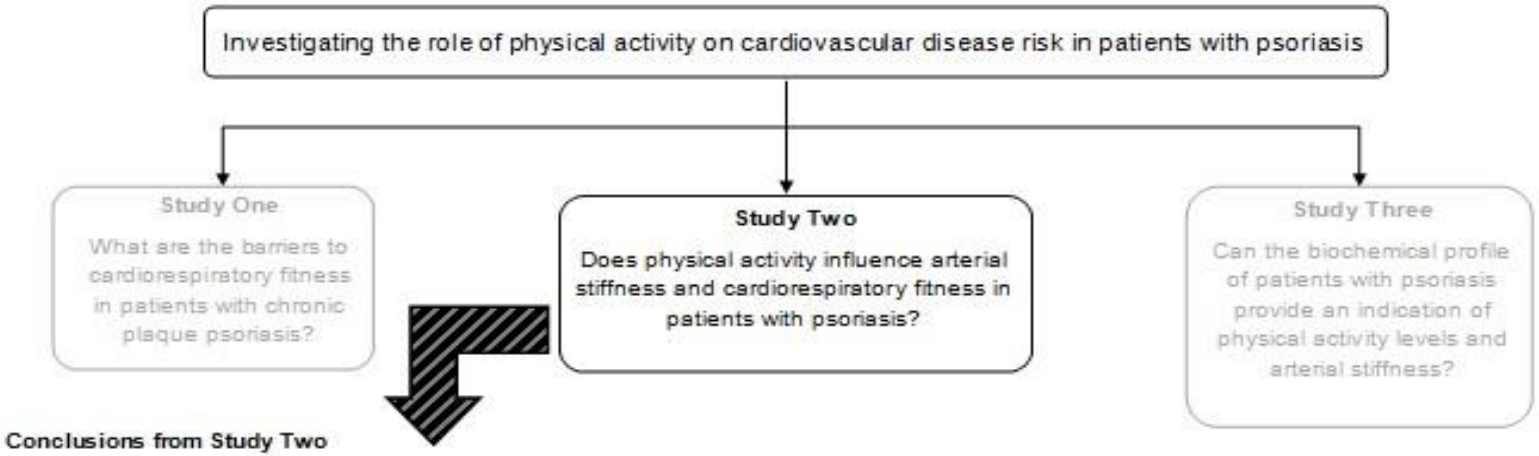
This is the first study to investigate the relationships between PWV, DRA and self-report patterns of activity, in a psoriasis population. The results from this study show that future CVD risk, as measured by PWV is closely correlated (inverse relationship) with cardiorespiratory fitness, as measured by the DRA. Additionally, the type of physical activity is a key factor in determining PWV. It was found that PWV and vigorous-intensity physical activity scores were significantly, inversely correlated, particularly in males with psoriasis, aged 18-65**.** These results imply that the quantity of energy expended during exercise is key for arterial stiffness and future CVD risk. Further examination of PWV amongst the 3 levels of activity (categorical IPAQ score) highlighted significant differences in PWV between categories 2 (moderate level of activity) and 3 (high level of activity), therefore emphasising the importance of the type and quantity of activity, particularly in individuals aged 18-65. Taking into account the relationship between vigorous-intensity activity and PWV, along with the cardiovascular disease risk in this group of patients, this aspect of patient management could be targeted for intervention.

The current study also found that cardiorespiratory fitness, (as measured by DRA) is significantly correlated with self-report levels of moderate and vigorous-intensity physical activity, particularly in males and females with psoriasis, aged 18-65. It is evident that the type of activity is a key factor in determining cardiorespiratory fitness in patients with psoriasis. DRA values also varied significantly between the low-levels (category 2) of activity and the high-levels of activity (category 3) groups in participants with psoriasis, aged 18-65 years. Additionally, DRA values were significantly lower in people with psoriasis, aged 18-65, who failed to meet the AHA guidelines for physical activity. The DRA was found to be sensitive to sedentary behaviour, particularly in females with psoriasis, aged 18-65. These results suggest that the DRA is potentially a surrogate measure for the amount of heart-healthy

exercise undertaken in the immediate several days/weeks. Although further calibration is required, DRA could be a means to ‘measure’ exercise and be a more objective way of doing so than a self-report tool.

Finally, the results from study three revealed that age, smoking and treatment for hypertension are significant predictors of arterial stiffness, as measured by PWV in patients with psoriasis. Age is also a significant predictor of cardiorespiratory fitness, as measured by DRA in this group of patients. These findings present specific factors to target in the psoriasis population (see figure 5.6.5 for a summary of the conclusions drawn from study two). These aspects of the current study will be discussed in more detail in chapter seven.

Figure 5.6.5 Summary of the main conclusions drawn from study two of this PhD.



Conclusions from Study Two

- This is the first study to investigate the relationships between PWV, DRA and self-report patterns of activity, in a psoriasis population.
- Heart health as measured by PWV is closely correlated with cardiorespiratory fitness, as measured by the DRA.
- The type of physical activity is a key factor in determining PWV. PWV and vigorous-intensity physical activity scores were significantly, inversely correlated, particularly in males with psoriasis, aged 18-65.
- These results imply that the quantity of energy expended during exercise is key for heart health.
- Taking into account the relationship between vigorous-intensity activity and heart health, along with the cardiovascular disease risk in this group of patients, this aspect of patient management could be targeted for intervention.
- Cardiorespiratory fitness, (as measured by DRA) is significantly correlated with self-report levels of moderate and vigorous-intensity physical activity, particularly in males and females with psoriasis, aged 18-65.
- The type of activity is a key factor in determining cardiorespiratory fitness in patients with psoriasis.
- The DRA is sensitive to sedentary behaviour, particularly in females with psoriasis, aged 18-65.
- These results suggest that the DRA is potentially a surrogate measure for the amount of heart-healthy exercise undertaken in the immediate several days/weeks. Although further calibration is required, DRA could be a means to 'measure' exercise and be a more objective way of doing so than a self-report tool.
- Age, smoking and treatment for hypertension are significant predictors of arterial stiffness, as measured by PWV, in patients with psoriasis.
- Age is a significant predictor of cardiorespiratory fitness, as measured by DRA, in patients with psoriasis.

CHAPTER SIX: CAN THE BIOCHEMICAL PROFILE OF PATIENTS WITH PSORIASIS PROVIDE AN INDICATION OF PHYSICAL ACTIVITY LEVELS AND ARTERIAL STIFFNESS?

6.1 Hypothesis

Blood levels of sE-selectin, metabolic biomarkers, circulatory lipids, adipokines and inflammatory biomarkers are indicative of cardiorespiratory fitness and arterial stiffness in patients with psoriasis, but can be influenced by physical activity.

6.2 Rationale

The aetiology of the increased risk of CVD observed in patients with psoriasis is likely to be complex and may be driven by an increased prevalence of risk factors such the metabolic syndrome (Kimball et al., 2008). The metabolic syndrome is a constellation of metabolic disturbances, all of which are known risk factors for CVD. These metabolic malfunctions include: glucose intolerance (e.g. Type 2 diabetes) or insulin resistance, hypertension, dyslipidaemia and abdominal obesity (Eckel et al., 2005, Kimball et al., 2008). Some studies have found that obesity is associated with increased risk of developing psoriasis as well as exacerbation of pre-existing disease (Sterry et al., 2007, Hamminga et al., 2006). In other studies body mass index (BMI) has been shown to correlate with clinical severity of psoriasis (Sterry et al., 2007, Hamminga et al., 2006, Huang et al., 2010). Hamminga et al also recognised that

weight loss in obese psoriasis patients can improve the clinical extent of the disease (Hamminga et al., 2006). Adipose tissue produces bioactive mediators, including adipokines which have numerous metabolic functions. For example, adipokines influence body weight homeostasis and insulin resistance as well as alterations in lipids, blood pressure and inflammation (Van Gaal et al., 2006). It is the dysregulation of adipokines such as resistin and adiponectin that, in obesity, contributes to chronic inflammation, the development of the metabolic syndrome and CVD (Maury and Brichard, 2010). Plasma levels of resistin have been shown, in small studies (n=<40), to correlate with PASI and to decrease following treatment of psoriasis (Corbetta et al., 2006, Boehncke et al., 2007b, Johnston et al., 2008, Coimbra et al., 2009)

Plasma levels of adiponectin are elevated in chronic inflammatory systemic diseases, such as rheumatoid arthritis and inflammatory bowel disease) (Fantuzzi, 2008).

Psoriasis and CVD are both immune-mediated inflammatory conditions and it has therefore been proposed that the process of inflammation may be an integral mechanistic link between them (Spah, 2008, Davidovici et al., 2010). Various cytokines, including TNF-α, and IL-6, are implicated in the pathogenesis of both psoriasis and CVD. TNF-α exerts powerful proinflammatory effects, including the upregulation of adhesion molecules such as E-selectin (Tracey et al., 2008, Kölliker Frers et al., 2015). E-selectin is required for the transepithelial migration of leukocytes and has also been implicated in the development of CVD (Hwang et al., 1997).

The increased risk of CVD in patients with psoriasis may be mediated through behaviourally driven cardiovascular risk factors such as smoking, depression and lack of physical activity (Kimball et al., 2008, Wilson et al., 2012). The focus of this study is physical activity and how it can influence the biochemical profile of patients with psoriasis. Taking into account the current literature, it was hypothesised that in patients with psoriasis: i) levels of sE-selectin, metabolic markers, inflammatory

markers, circulatory lipids, adipokines (specifically leptin and resistin) would be inversely correlated with physical activity and ii) these biomarkers would correlate with arterial stiffness (PWV), a pre-clinical marker of future cardiovascular events, therefore potentially providing an opportunity to identify asymptomatic individuals at greatest risk of morbidity and mortality.

6.3 Results

6.3.1 Subjects characteristics

Of the 117 subjects (recruited from the psoriasis clinic at Salford Royal Hospital; a tertiary referral psoriasis clinic) who took part, a median age of 42 was observed (IQR: 33-49) with 56.4% males and 43.6% females. All participants were identified as having chronic plaque psoriasis, 65% had a family history of the disease. The median PASI was 4.4 (IQR:1.9-8). Table 6.1 presents the characteristics of participants in this study. The median and IQR are presented for continuous variables and percentages are presented for categorical variables.

Table 6.1 Characteristics of study subjects.

	Study Group 3 (n=117)	Males (n=66)	Females (n=51)
Age	42 (33-49)	43 (35.3-49)	40 (30-50)
Weight (kg)	84.1 (67.5-97.3)	90.3 (79.6-104.4)	72.4 (63.3-87.7)
BMI	27.6 (24-32)	28.3 (25-32.3)	26.4 (23.2-31.6)
PASI	4.4 (1.9-8)	5.5 (2.7-9.2)	2.7 (1.2-5.4)
DLQI	5 (2-8)	6 (2-10)	3 (1-6)
Myocardial infarction (%)	0.9	0	2
Atrial fibrillation (%)	4.3	4.5	3.9
Angina (%)	1.7	3	0
Stroke (%)	0	0	0
Transient ischaemic attack (%)	0	0	0
Treatment for hypertension (%)	18.8	18.2	19.6
Family history of premature CHD (%)	24.6	30.3	18.4
Psoriatic arthritis (%)	30.4	31.3	29.4
Rheumatoid arthritis (%)	6.1	6.3	5.9
Diabetes (%)	6	6.1	5.9
Treatment with lipid-lowering medication (%)	7.8	9.1	5.9
Smoker (%)	31	20	11
Systemic treatment (%)	48	52	43
Total IPAQ score (MET-mins/week)	1865.3 (694.8-4156.5)	1899 (742.5-5148)	1777.5 (660-3384.8)
Walking score (MET-mins/week)	742.5 (264-2376)	742.5 (280.5-2772)	693 (264-1707.8)
Moderate-intensity activity score (MET-mins/week)	0 (0-715)	100 (0-840)	0 (0-480)
Vigorous-intensity activity score (MET-mins/week)	280 (0-1440)	400 (0-1560)	120 (0-1080)
IPAQ category 1 (%)	22.7	19.4	27.1
IPAQ category 2 (%)	32.7	38.7	25
IPAQ category 3 (%)	44.5	41.9	47.9
AHA guidelines (% who adhere)	51.8	56.9	44.7
PWV	7.4 (6.2-8.8)	7.4 (6.2-8.7)	7.6 (6.3-9.5)
DRA	47 (42-57.8)	48 (43-58)	47 (40-57)

6.3.2 sE-selectin

6.3.2.1 sE-selectin was significantly, inversely correlated with vigorous-intensity physical activity scores in males with psoriasis

E-selectin is a cellular adhesion molecule which is expressed on activated endothelial cells. The function of E-selectin is to facilitate leukocyte rolling, adhesion and transmigration into the sub-endothelial space (Natarajan et al., 2011). Hence, it is believed that this molecule may act as a pre-clinical marker of endothelial dysfunction.

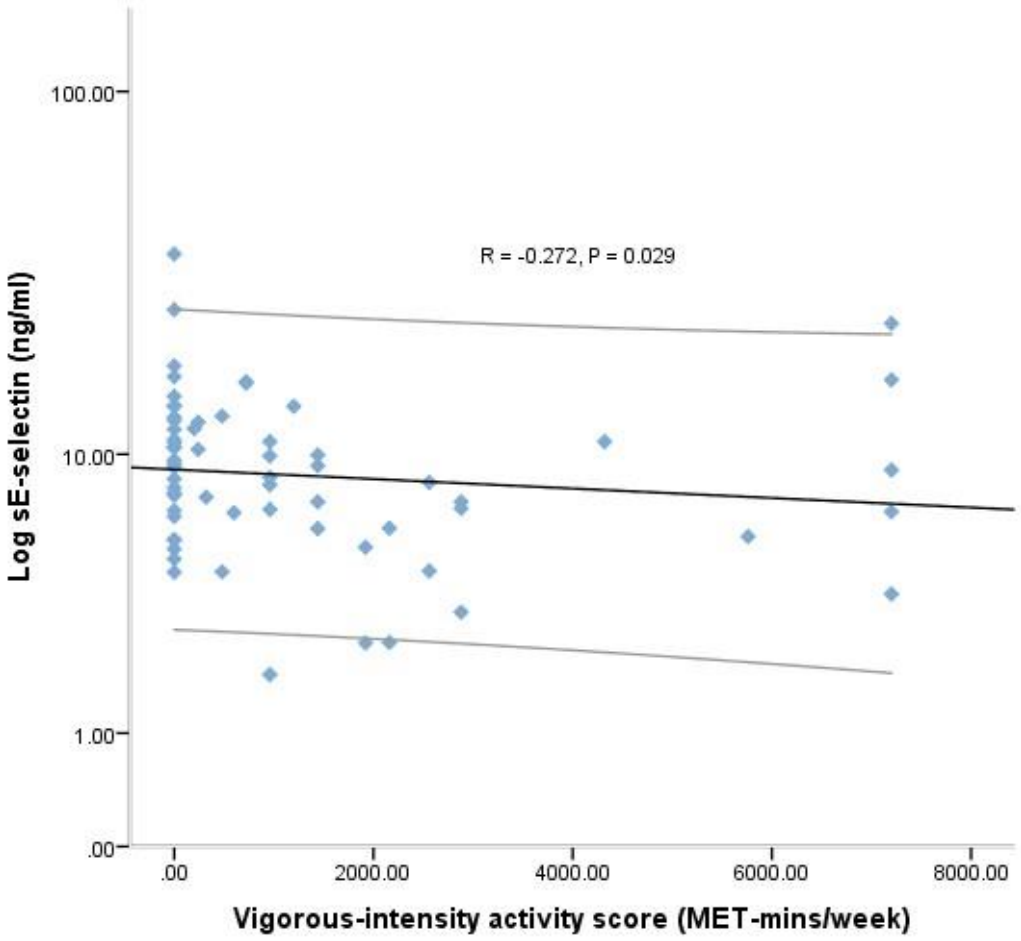
These analyses address the following specific hypothesis: there will be a significant, negative correlation between sE-selectin and self-reported patterns of physical activity. The beneficial effects of increased physical activity include a reduction of vessel wall inflammation (Abramson and Vaccarino, 2002) and prothrombotic activity (Womack et al., 2003).

Spearman correlation analyses were performed in order to assess the relationship between sE-selectin and self-reported patterns of physical activity. Assessment of the study group revealed that there was no significant correlation between sE-selectin and the IPAQ parameters.

Examination of gender differences identified a significant negative correlation between sE-selectin and vigorous-intensity physical activity in males ($r = - 0.272$, $p = 0.029$). Therefore, as the activity scores increased, levels of sE-selectin decreased. Conversely, no significant correlations between sE-selectin and activity were observed in the female population.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Figure 6.6.2.1 Vigorous-intensity physical activity was significantly correlated with plasma levels of sE-selectin in males with psoriasis (n=64)



The scatter plot above depicts the correlation between sE-selectin and vigorous-intensity physical activity in males with psoriasis. The significant inverse correlation indicates that the higher the level of physical activity, the lower the sE-selectin concentration. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. sE-selectin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 3%; missing cases were excluded pairwise.

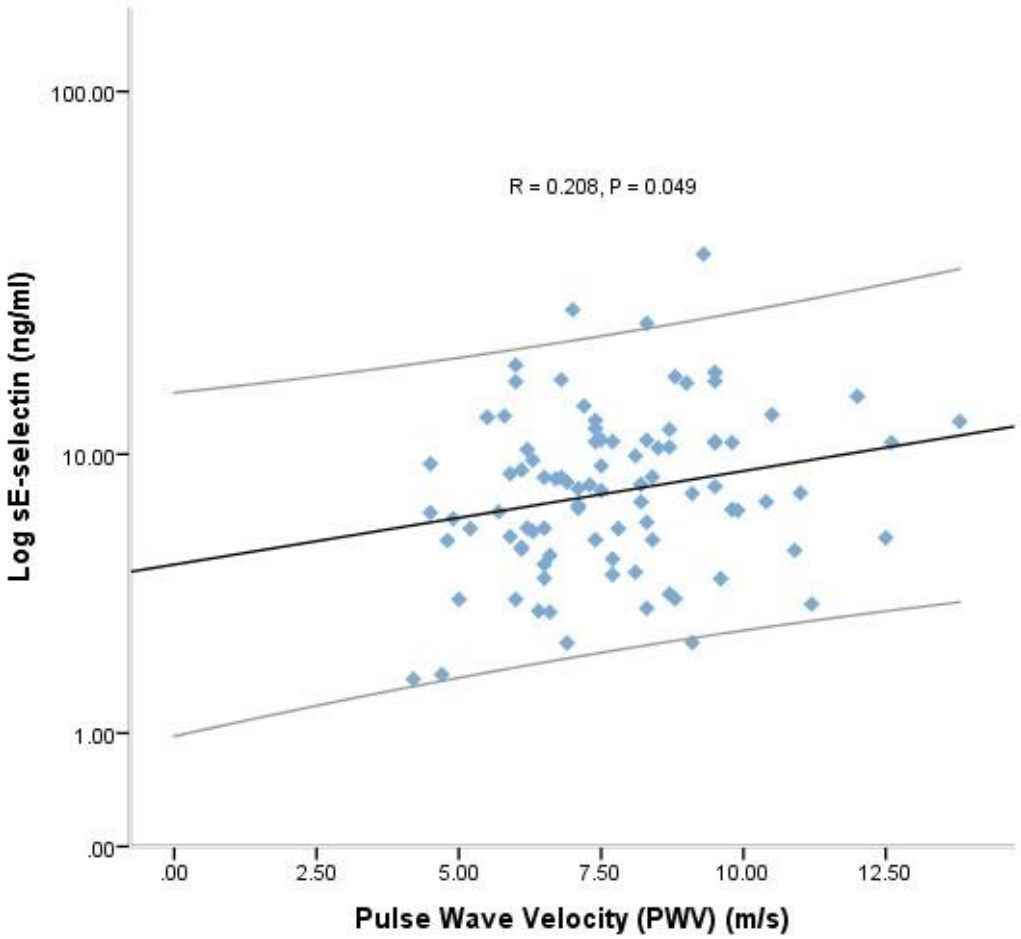
6.3.2.2 sE-selectin was significantly correlated with PWV in people with psoriasis

A Spearman correlation analysis was carried out in order to assess the relationship between levels of sE-selectin and PWV. These analyses address the following specific hypothesis: there will be a significant correlation between arterial stiffness (PWV) and sE-selectin.

Assessment of the study group revealed a significant correlation between PWV and plasma levels of sE-selectin ($r = 0.208$, $p = 0.049$). This finding was not significant following a sensitivity analysis which excluded patients with psoriatic arthritis.

Examination of gender differences, however, found no significant correlations between PWV and sE-selectin.

Figure 6.6.2.2 Pulse wave velocity was significantly correlated with plasma levels of sE-selectin in patients with psoriasis (n=90)



The scatter plot above highlights the correlation between PWV and sE-selectin concentration in patients with psoriasis. The significant positive correlation indicates that PWV values increase with increasing levels of sE-selectin. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. sE-selectin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 23%; missing cases were excluded pairwise.

6.2.2.3 There was no relationship between sE-selectin and DRA in people with psoriasis

A Spearman correlation analysis was carried out in order to examine the relationship between plasma levels of sE-selectin and DRA. The DRA is a dimensionless index that is thought to provide an indication of an individual's cardiorespiratory fitness. The higher the DRA value, the more active people are likely to be. These analyses addressed the following specific hypothesis: there will be a significant inverse correlation between cardiorespiratory fitness (DRA) and sE-selectin.

Assessment of the study group revealed no significant correlation between plasma levels of plasma sE-selectin and DRA. Examination of gender differences also revealed no significant correlations between sE-selectin levels and DRA.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

6.3.2.4 Concentrations of sE-selectin did not vary significantly between those who adhered to the AHA guidelines for physical activity and those who did not

Independent samples t-tests were used to detect differences in plasma levels of sE-selectin between those who met the AHA guidelines for physical activity and those who did not.

Assessment of the study group showed no significant difference in sE-selectin levels between those who met the AHA guidelines for physical activity and those who did not. Examination of gender differences also revealed no significant differences.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Table 6.6.2.1 Mean sE-selectin levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of sE-selectin (ng/ml)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	8.3 (0.6)	8.7 (0.8)	7.3 (1.0)
AHA guidelines for physical activity not met	9.5 (0.8)	11.5 (1.3)	7.2 (0.8)

Results are presented as means with standard error of the mean in brackets.

6.3.2.5 sE-selectin was significantly correlated with PASI

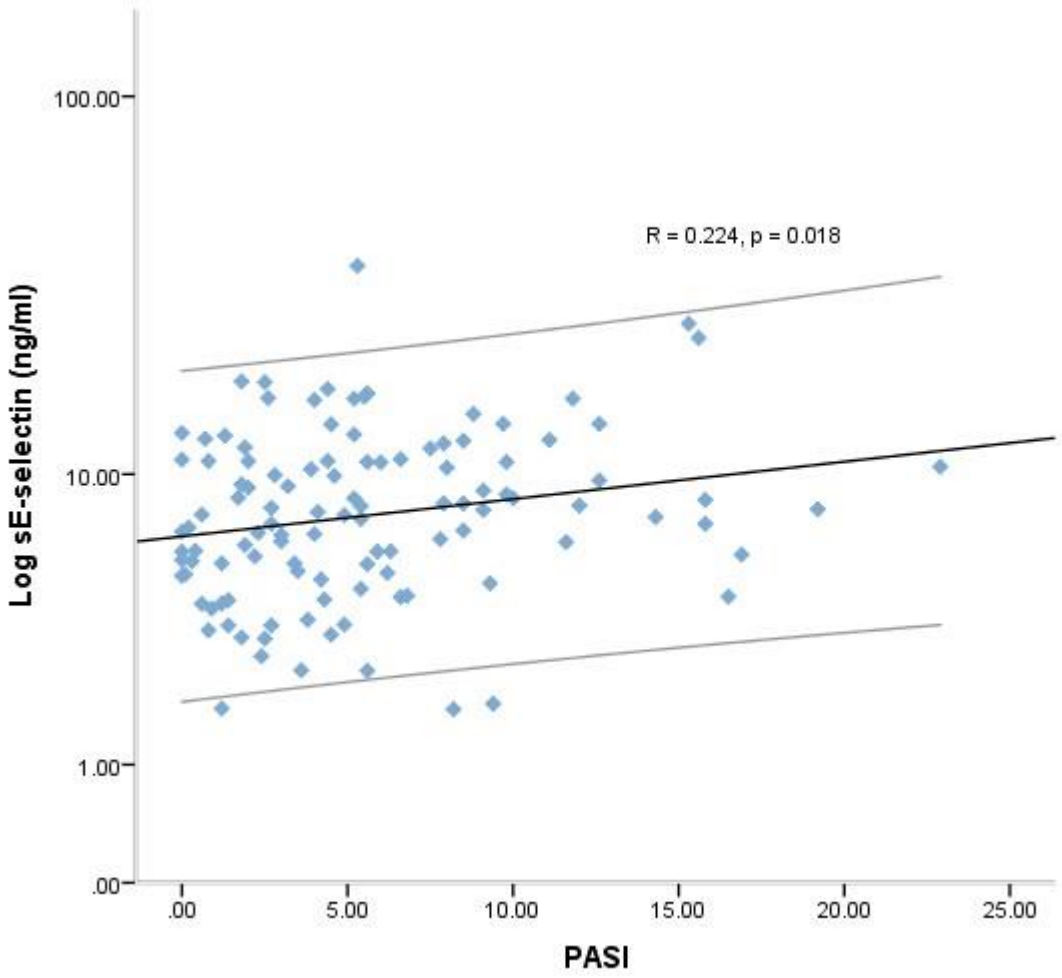
A Spearman correlation analysis was carried out in order to assess the relationship between sE-selectin and psoriasis. Previous work has shown that sE-selectin correlates with PASI (Szepietowski et al., 1999, Czech et al., 1996). These analyses address the following specific hypothesis: there will be a significant correlation between psoriasis severity, as assessed by the PASI and sE-selectin.

Assessment of the study group revealed a significant correlation between sE-selectin concentration and PASI ($r = 0.224$, $p = 0.018$).

However, individual examination of males and females showed no significant correlation between these two variables.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Figure 6.6.2.5 Levels of sE-selectin were significantly correlated with PASI in patients with psoriasis (n=112)



The scatter plot above highlights the correlation between PASI and levels of sE-selectin in patients with psoriasis. The significant positive correlation indicates that PASI values increase with increasing levels of sE-selectin. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. sE-selectin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 4.3%; missing cases were excluded pairwise.

6.3.3 Metabolic markers: fasting glucose, insulin and HbA1C

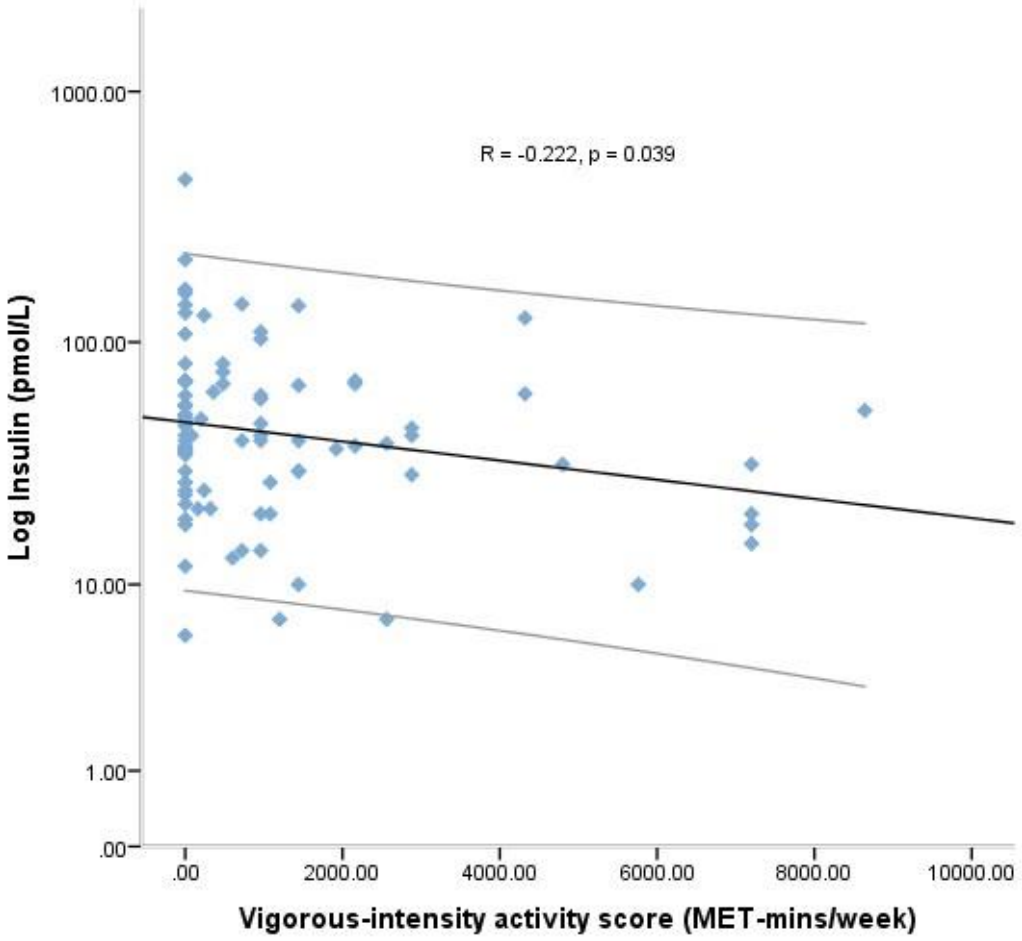
For the purpose of the analyses presented in this section participants with diabetes or those currently on lipid lowering medication were excluded.

6.3.3.1 Insulin was significantly, inversely correlated with physical activity in people with psoriasis

Previous studies have shown that physical activity, particularly high-intensity activity, improves blood glucose levels and insulin sensitivity in both diabetics and non-diabetics (Adams, 2013). It has also been established that physical activity can reduce blood levels of HbA1C in both, patients with type 2 diabetes (Bweir et al., 2009), and healthy controls (Mora et al., 2007). These analyses address the following specific hypothesis: there will be significant, inverse correlations between concentrations of metabolic markers and self-reported levels of physical activity. For the purpose of the analyses, levels of insulin were measured in combination with levels of HbA1C in order to provide an overall assessment of insulin resistance. A previous study showed that HbA1C concentration can be used as an effective screening tool to detect insulin sensitivity and resistance at an early stage, in a population of obese children, when compared with the homeostasis model assessment (HOMA-IR) index (Önal et al., 2014)

Assessment of the study group revealed no significant correlations for fasting glucose or HbA1C. However, a significant negative correlation was identified between levels of insulin and vigorous-intensity activity ($r = -0.222$, $p = 0.039$). Therefore, as activity scores increased, insulin levels decreased.

Figure 6.6.3.1 Vigorous-intensity physical activity was significantly, inversely correlated with insulin concentrations in patients with psoriasis (n=101)

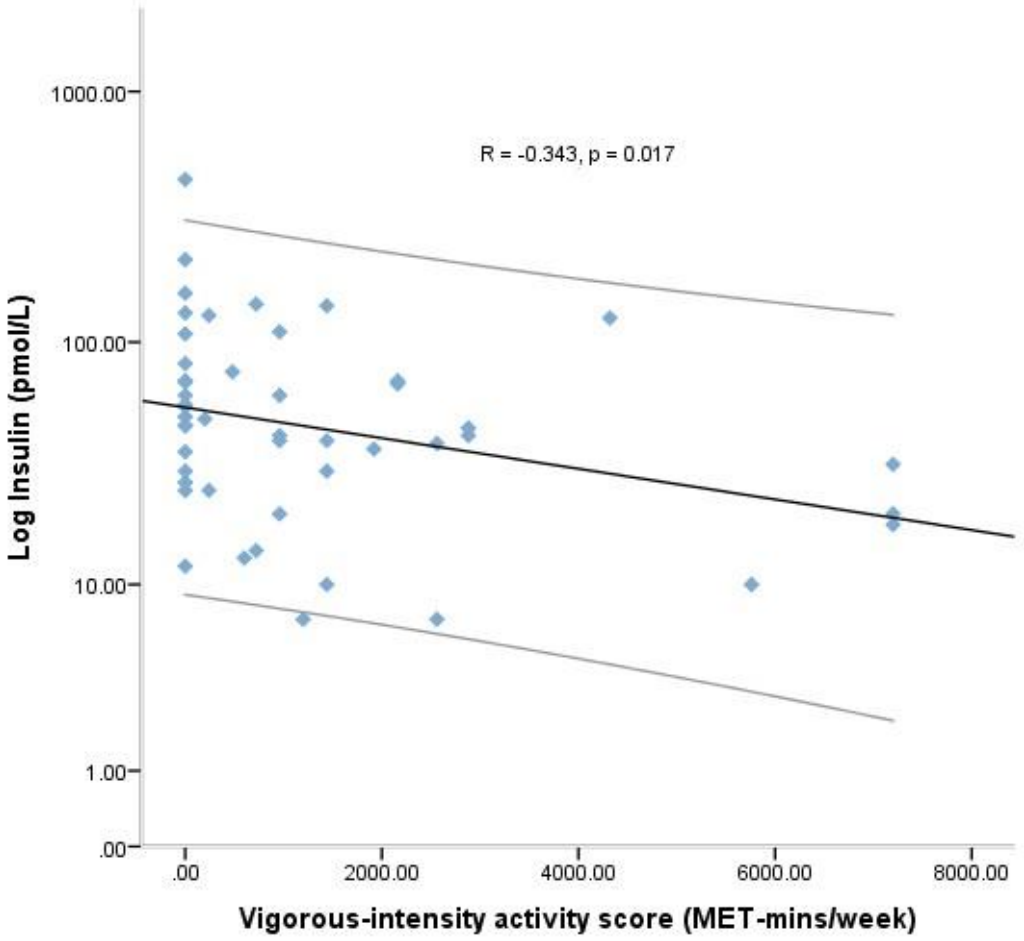


The scatter plot highlights the correlation between insulin and vigorous-intensity physical activity in patients with psoriasis. The significant negative correlation indicates that the higher the level of vigorous-intensity physical activity, the lower insulin concentration. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Insulin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 13.7%; missing cases were excluded pairwise.

Subsequent examination of gender differences revealed a significant negative correlation between levels of insulin and vigorous-intensity physical activity in males

($r = -0.343$, $p = 0.017$). Therefore, as vigorous-intensity physical activity scores increased, insulin levels decreased. Both fasting glucose and HbA1C levels showed no significant correlations with physical activity in male participants.

Figure 6.6.3.2 Vigorous-intensity physical activity was significantly, inversely correlated with levels of insulin in males with psoriasis (n=56)



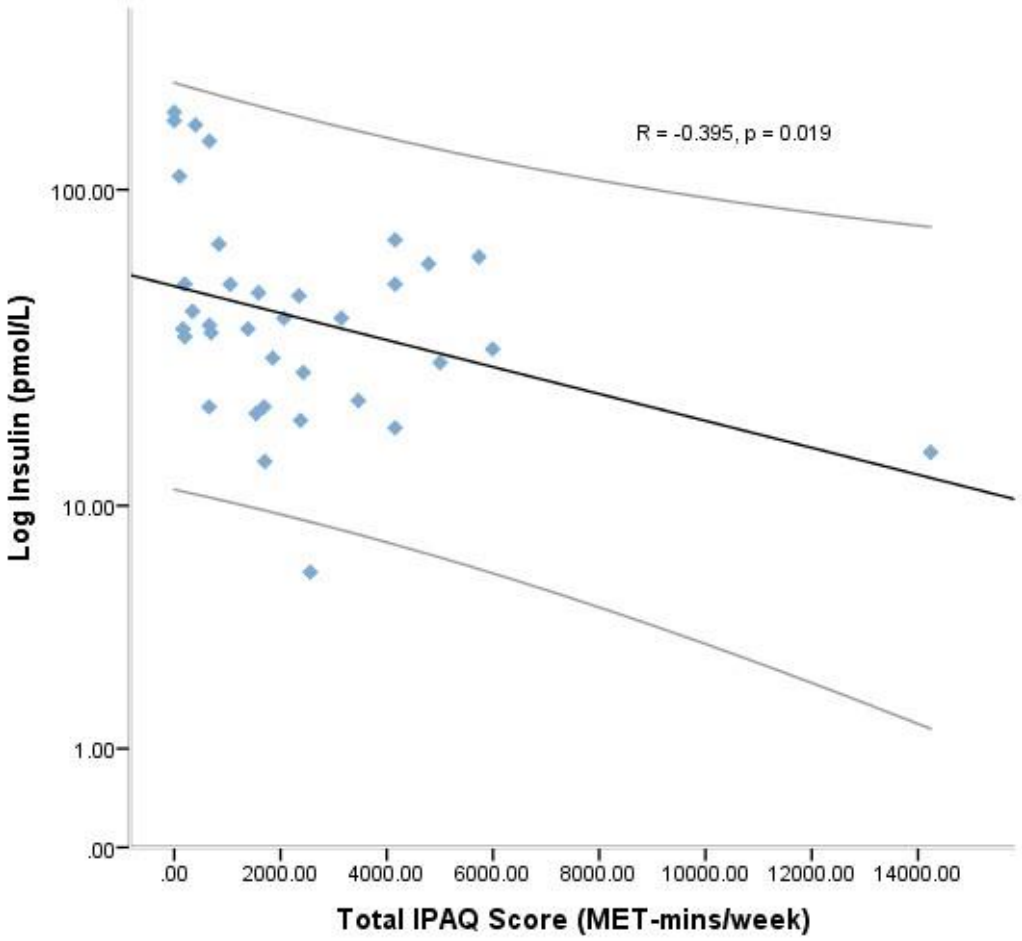
The scatter plot represents the correlation between vigorous-intensity physical activity and insulin levels in males with psoriasis. The significant inverse correlation between these two variables indicates that vigorous-intensity activity can help to reduce insulin levels in this group of patients. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Insulin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 15.2%; missing cases were excluded pairwise.

Upon examination of the female cohort, significant negative correlations were observed between: insulin and total IPAQ scores ($r = -0.395$, $p = 0.019$) and insulin and walking scores ($r = -0.407$, $p = 0.012$). Significant negative correlations were also observed between fasting glucose levels and total IPAQ scores ($r = -0.501$, $p = 0.002$) and fasting glucose and walking scores ($r = -0.361$, $p = 0.028$) in females. Therefore, as activity scores increased, levels of these biomarkers decreased.

The relationships between insulin and total IPAQ scores and insulin and walking scores, in females, were not significant following sensitivity analyses which excluded patients with psoriatic arthritis.

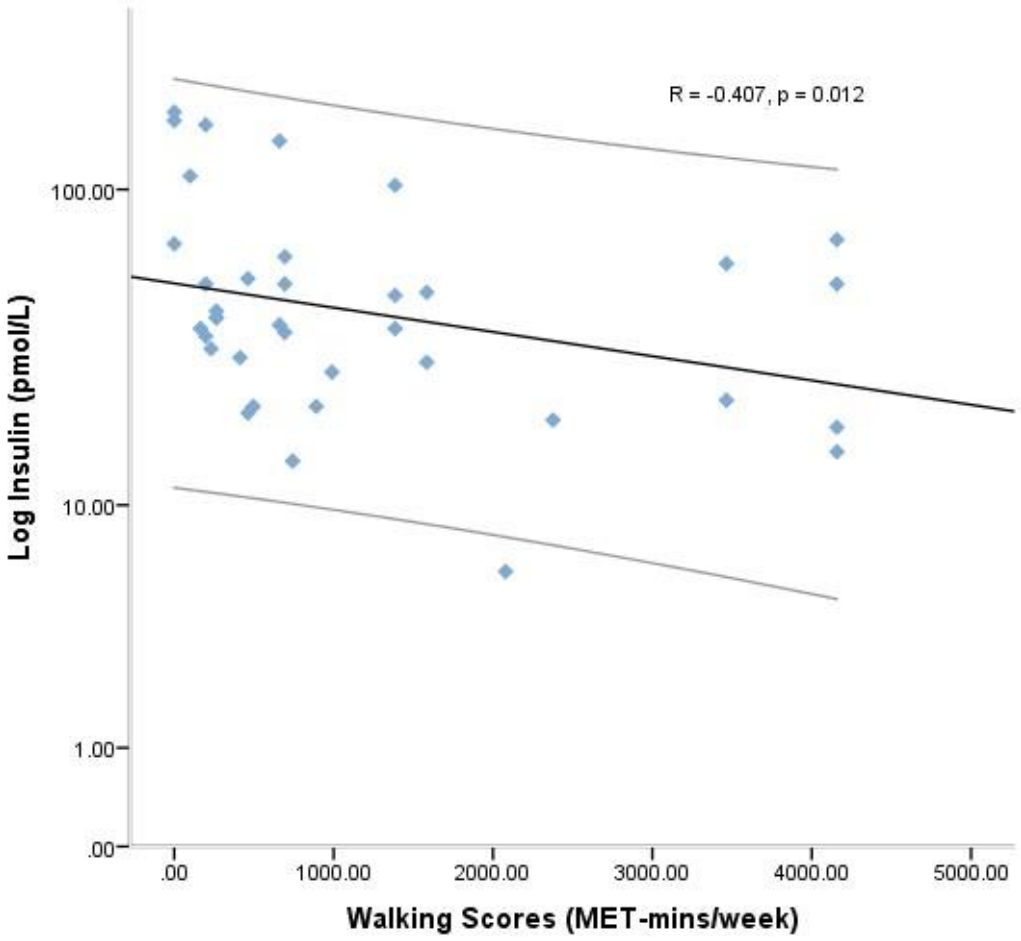
It is important to take into consideration that the presence of psoriatic arthritis may impede a patient's ability to engage in physical activity. This will be further discussed in chapter 7 of this thesis.

Figure 6.6.3.3 Physical activity was significantly, inversely correlated with insulin levels in females with psoriasis (n=40)



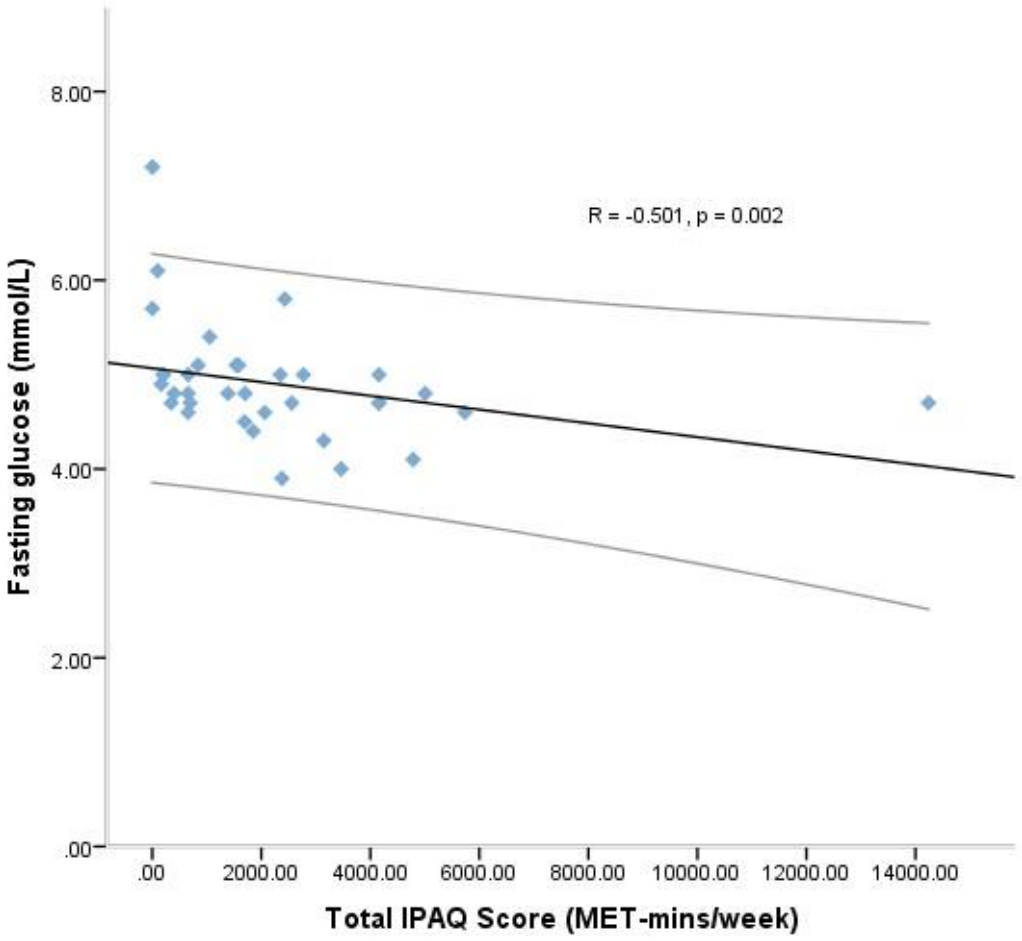
The scatter plot presents the correlation between physical activity and insulin levels in females with psoriasis. The significant inverse correlation between these two variables indicates that physical activity can help to reduce insulin levels in this group of patients. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Insulin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 21.6%; missing cases were excluded pairwise.

Figure 6.6.3.4 Mild physical activity (walking) was significantly, inversely correlated with insulin levels in females with psoriasis (n=42)



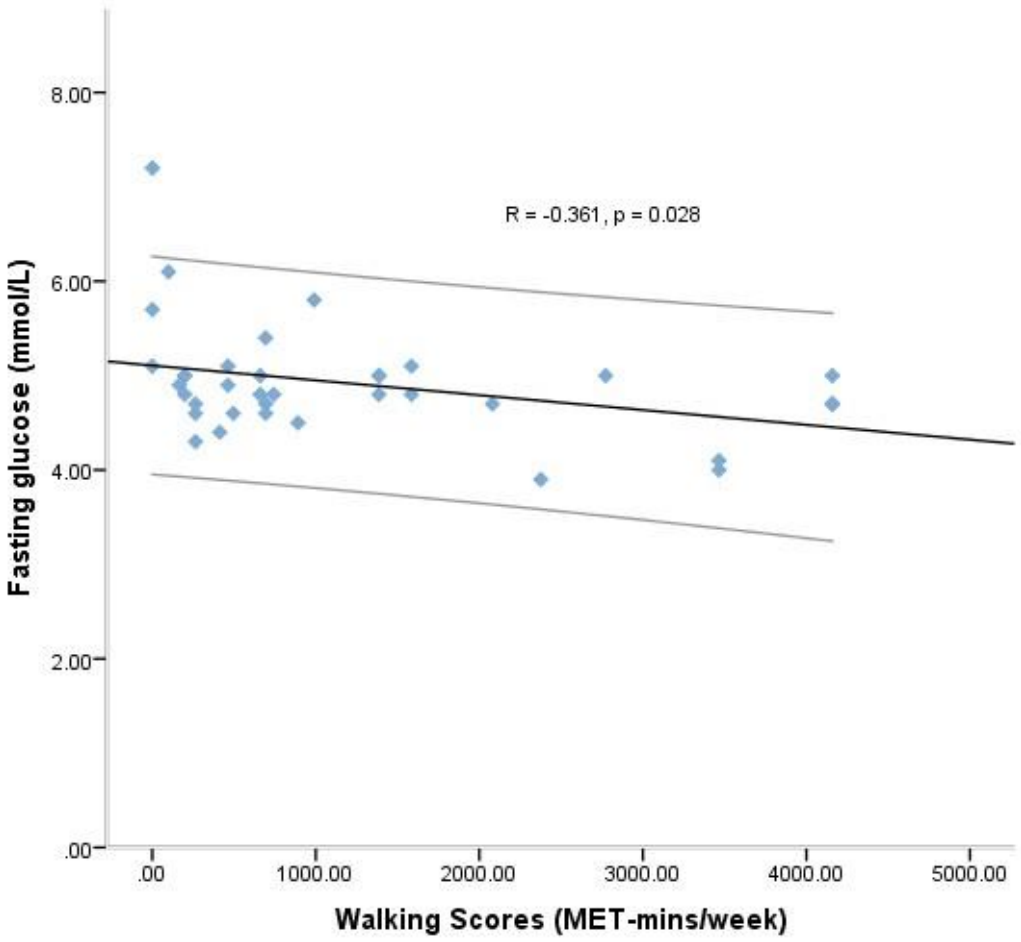
The scatter plot depicts the correlation between mild-intensity physical activity and insulin levels in females with psoriasis. The significant inverse correlation between these two variables indicates that insulin levels become lower with increasing levels of physical activity. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Insulin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 17.6%; missing cases were excluded pairwise.

Figure 6.6.3.5 Physical activity was significantly, inversely correlated with fasting-glucose levels in females with psoriasis (n=39)



The scatter plot highlights the correlation between physical activity and fasting-glucose levels in females with psoriasis. The significant inverse correlation between these two variables indicates that physical activity can help to reduce fasting-glucose levels in this group of patients. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 23.5%; missing cases were excluded pairwise.

Figure 6.6.3.6 Mild-intensity physical activity (walking) scores were significantly, inversely correlated with fasting-glucose levels in females with psoriasis (n=41)



The scatter plot highlights the correlation between mild-intensity physical activity (walking) and fasting-glucose levels in females with psoriasis. The significant inverse correlation between these two variables indicates that physical activity can help to reduce fasting-glucose levels in this group of patients. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 19.6%; missing cases were excluded pairwise.

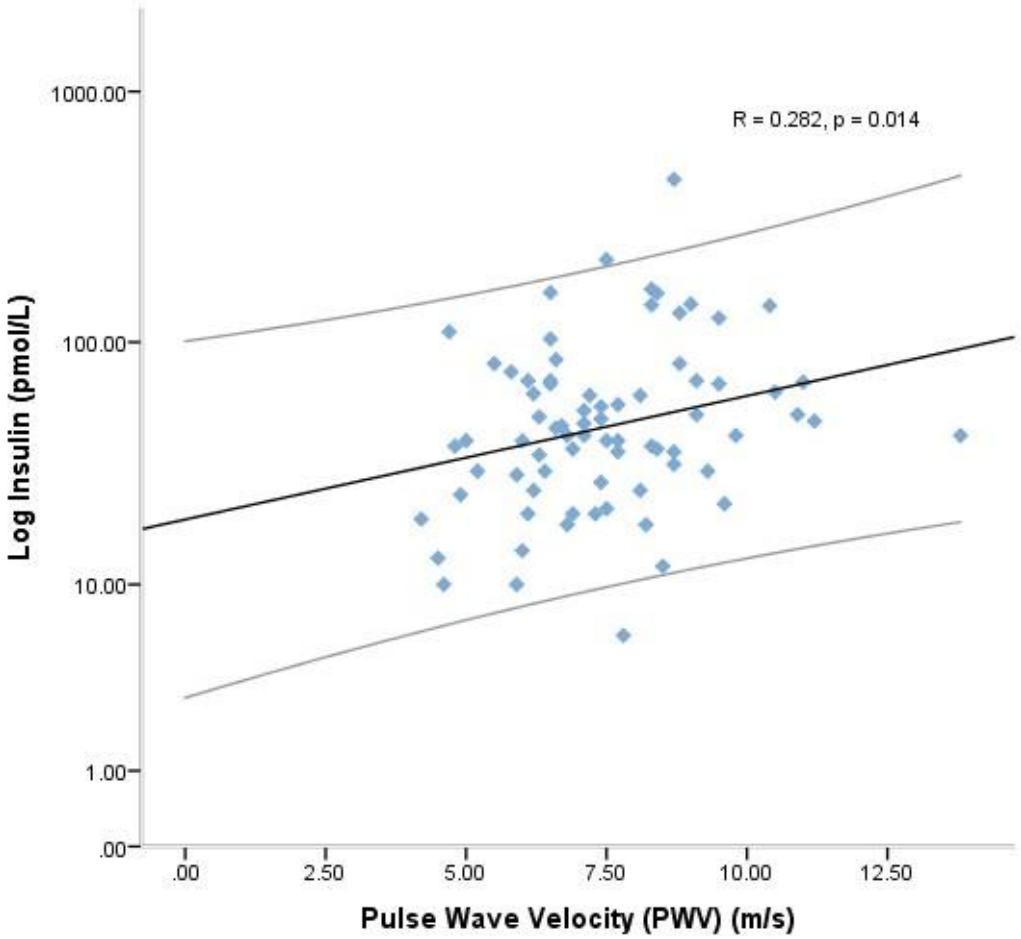
6.3.3.2 Insulin was significantly correlated with PWV in males with psoriasis, whilst fasting glucose was significantly correlated with PWV in females with psoriasis

It has been established that increased levels of metabolic markers are associated with increased risk of arterial stiffness (Salomaa et al., 1995, Shin et al., 2011).

These analyses address the following specific hypothesis: there will be a significant positive correlation between arterial stiffness (PWV) and levels of fasting glucose, insulin and HbA1C.

Assessment of the study group revealed a significant correlation between insulin levels and PWV ($r = 0.282$, $p = 0.014$). This finding was not significant following a sensitivity analysis which excluded patients with psoriatic arthritis.

Figure 6.6.3.7 Pulse wave velocity was significantly correlated with insulin levels in patients with psoriasis (n=84)

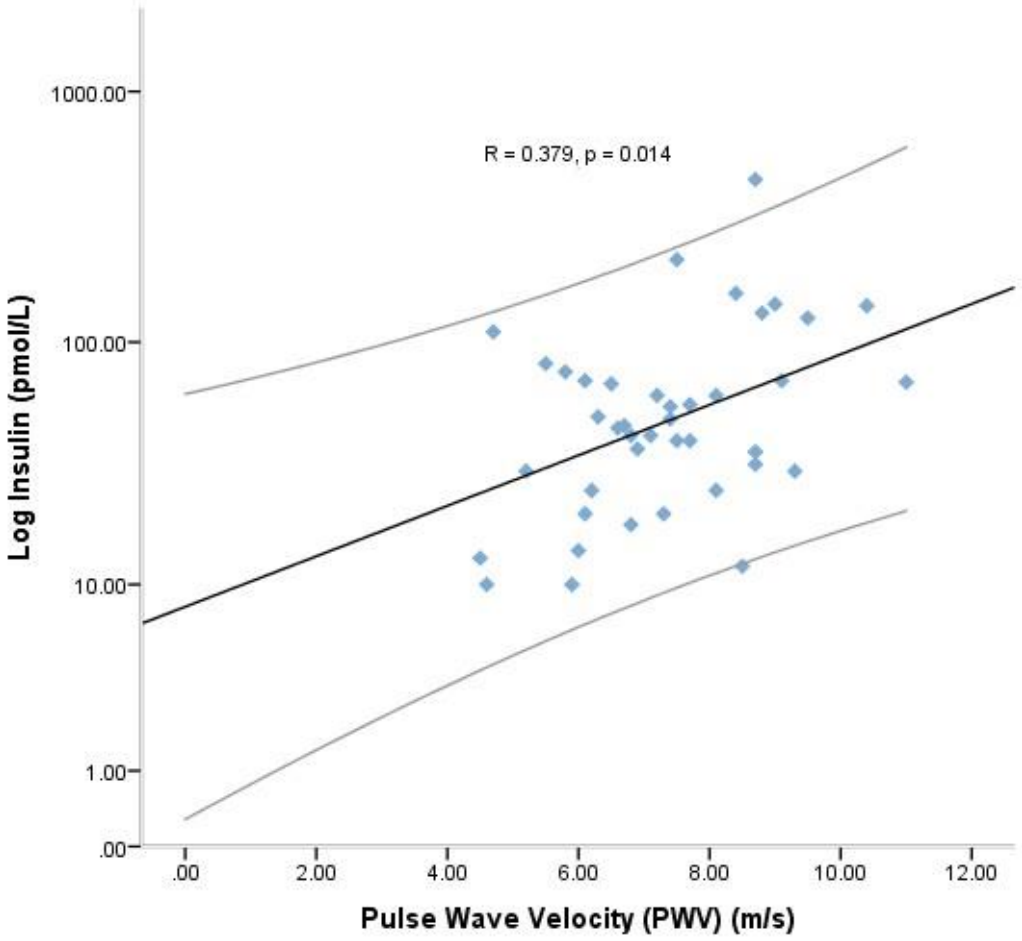


The scatter plot above presents the correlation between arterial stiffness (PWV) and insulin levels in patients with psoriasis. The significant positive correlation indicates that the higher one's insulin level is, the greater their PWV value may be. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Insulin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 28.2%; missing cases were excluded pairwise.

Examination of gender differences revealed that insulin levels were significantly correlated with PWV in males ($r = 0.379$, $p = 0.014$). This finding was not significant following a sensitivity analysis which excluded patients with psoriatic arthritis.

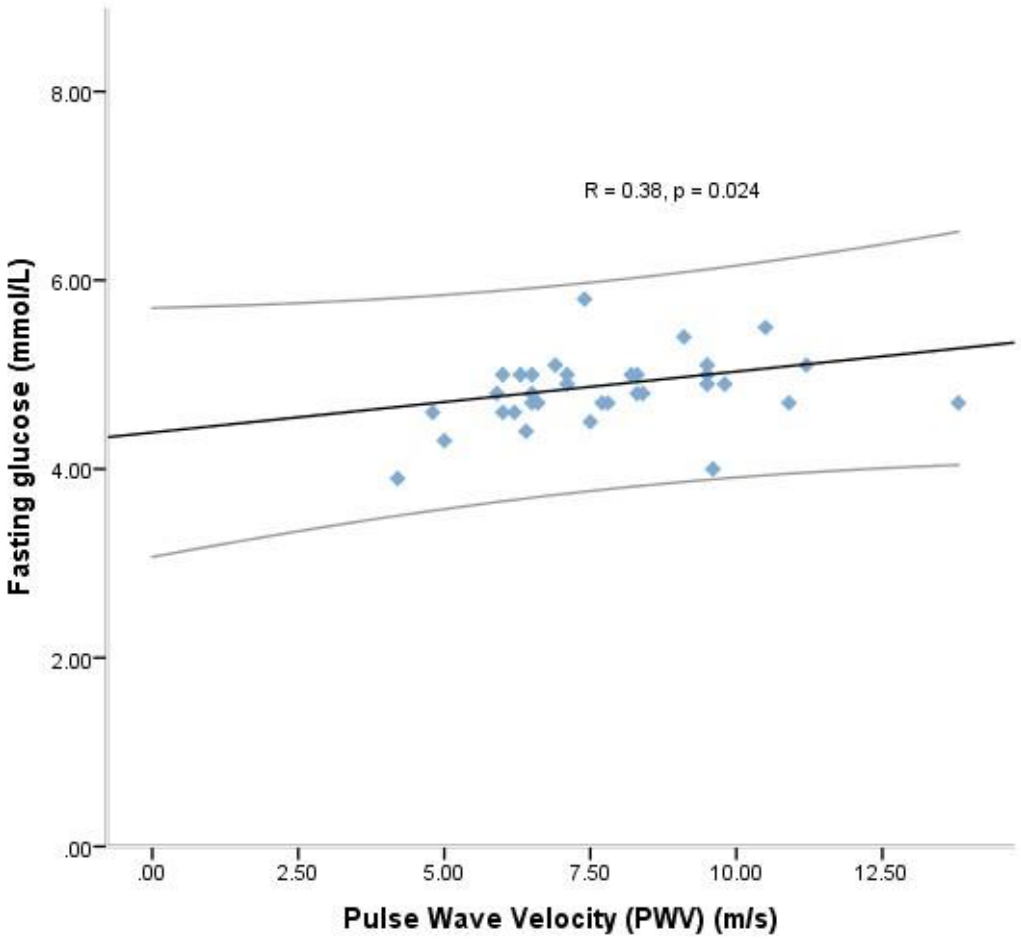
In females, a significant correlation was observed between fasting glucose levels and PWV ($r = 0.38$, $p = 0.024$). This finding was not significant following a sensitivity analysis which excluded patients with psoriatic arthritis.

Figure 6.6.3.8 Pulse wave velocity was significantly correlated with insulin levels in males with psoriasis (n=46)



The scatter plot above presents the correlation between arterial stiffness (PWV) and insulin levels in males with psoriasis. The significant positive correlation indicates that insulin levels may provide an indication of a person's PWV value. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Insulin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 30.3%; missing cases were excluded pairwise.

Figure 6.6.3.9 Pulse wave velocity was significantly correlated with fasting-glucose levels in females with psoriasis (n=39)



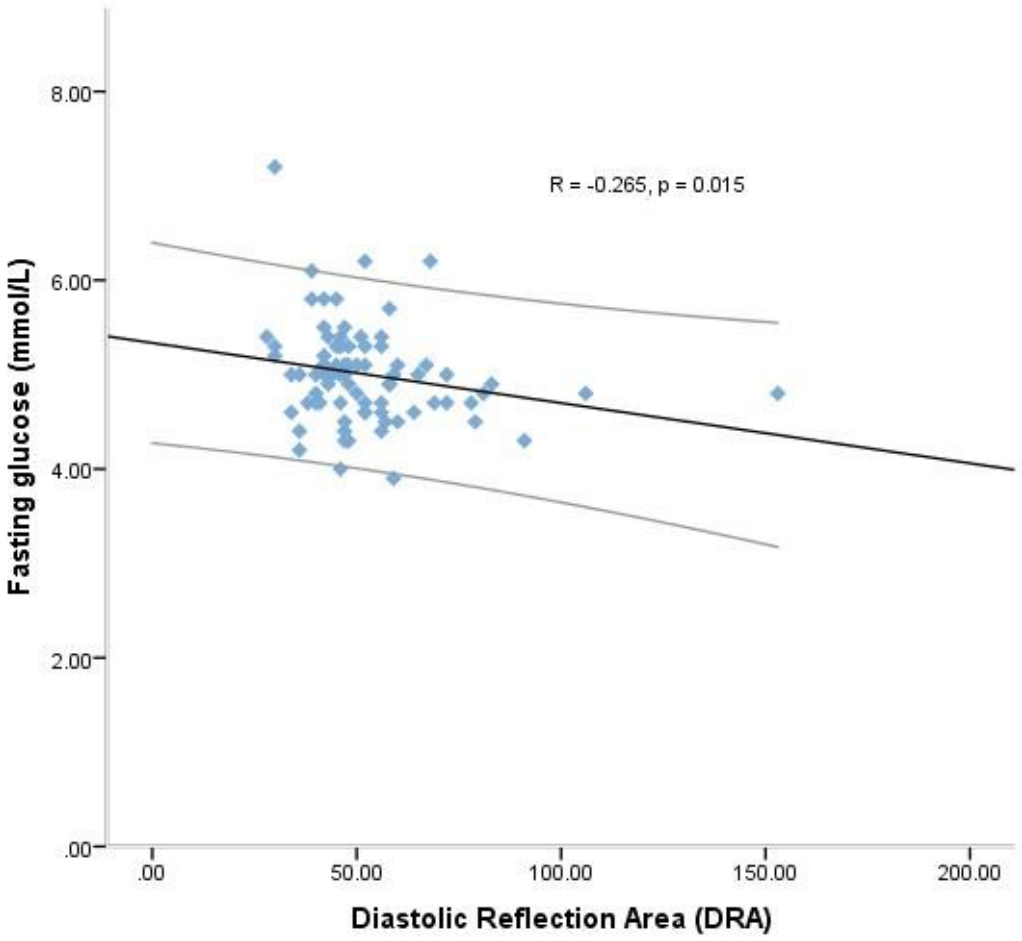
The scatter plot highlights the correlation between PWV and fasting-glucose levels in females with psoriasis. The significant positive correlation may suggest that fasting-glucose concentration provides an indication of one's PWV value. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 23.5%; missing cases were excluded pairwise.

6.3.3.3 Fasting glucose concentrations were significantly, inversely correlated with DRA values in females with psoriasis

DRA is an indicator of cardiac fitness and the higher the DRA value is; the greater an individual's cardiac fitness is likely to be. It has been established that physical activity can help to reduce levels of insulin, fasting plasma glucose and HbA1C. These analyses address the following specific hypothesis: there will be significant inverse correlations between cardiorespiratory fitness (DRA) and levels of metabolic markers.

Assessment of the study group revealed a significant negative correlation between fasting plasma glucose and DRA ($r = -0.265$, $p = 0.015$). Therefore, as DRA values increased, fasting glucose levels decreased. Sensitivity analyses, excluding patients with psoriatic arthritis also revealed a significant inverse correlation between HbA1C and DRA ($r = -0.31$, $p = 0.02$). However, all other results remained unchanged following sensitivity analyses.

Figure 6.6.3.10 Diastolic reflection area was significantly, inversely correlated with fasting-glucose levels in patients with psoriasis (n=94)

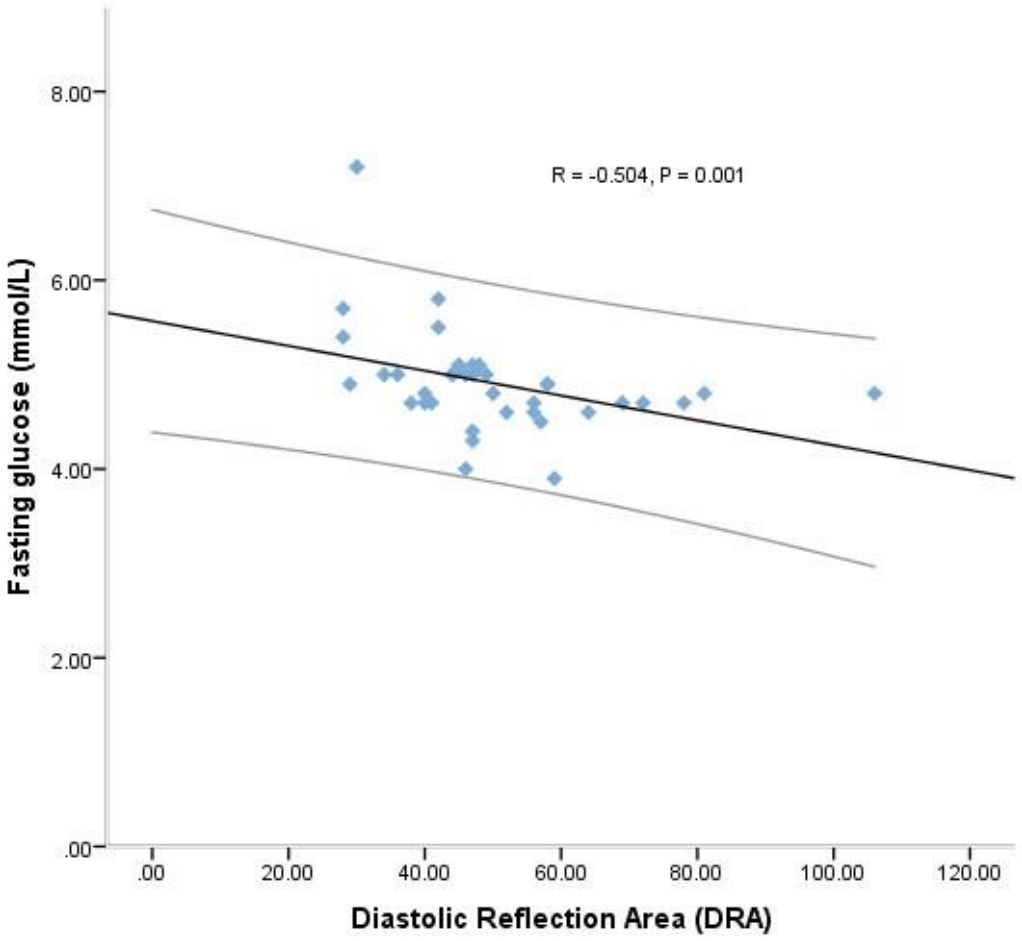


The scatter plot above depicts the correlation between DRA and fasting-glucose levels in study group 3. The significant inverse correlation indicates that DRA values increase as fasting-glucose levels reduce. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 19.7%; missing cases were excluded pairwise.

Examination of gender differences showed no relationship between levels of metabolic markers and DRA in males. Sensitivity analyses, excluding male patients with psoriatic arthritis revealed significant inverse correlations between HbA1C and DRA (r = -0.472. p = 0.005) and fasting glucose and DRA (r = -0.38, p = 0.032).

In females, a significant negative correlation was observed between fasting glucose levels and DRA ($r = -0.504$, $p = 0.001$). Therefore, as DRA values increased, fasting glucose levels decreased.

Figure 6.6.3.11 Diastolic reflection area was significantly, inversely correlated with fasting-glucose levels in females with psoriasis (n=41)

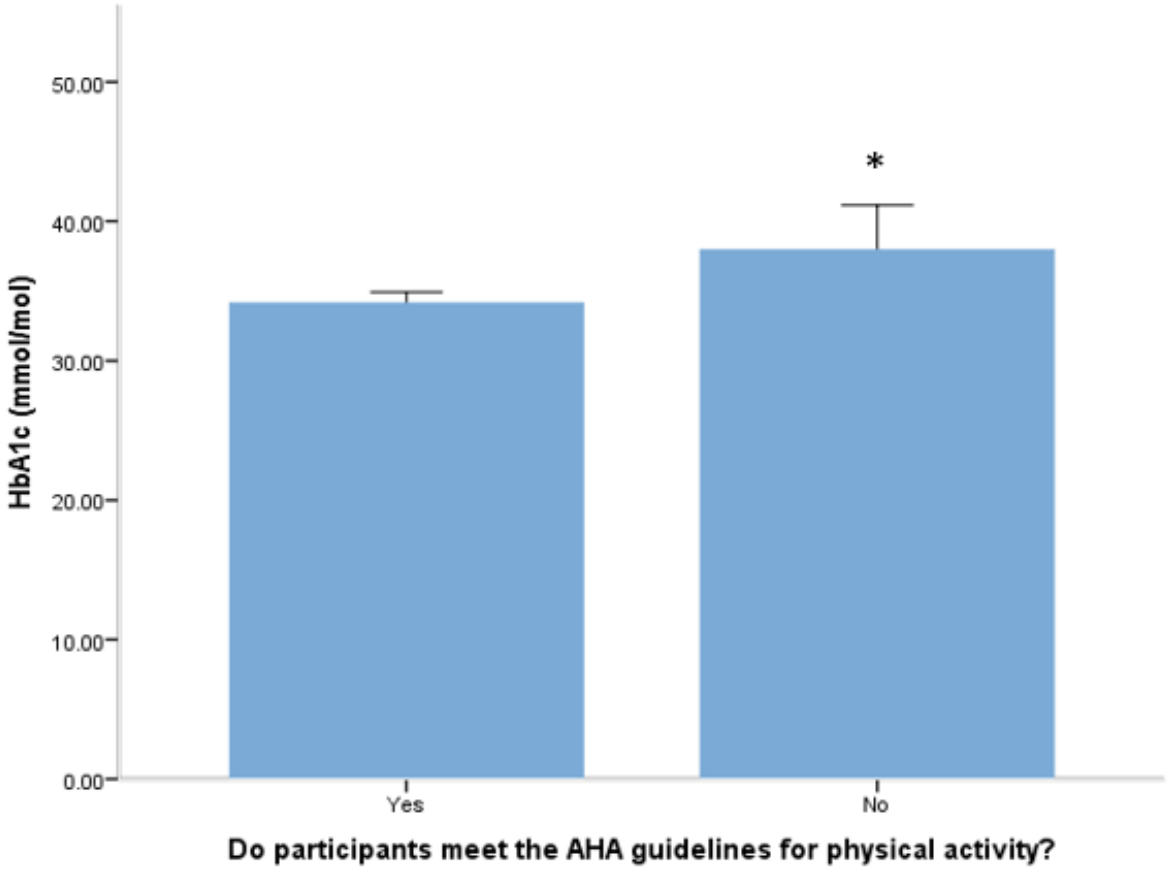


The scatter plot above highlights the correlation between DRA and fasting-glucose levels in females with psoriasis. The significant negative correlation indicates that DRA values increase as fasting-glucose levels reduce in this group of patients. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Missing data: 19.6%; missing cases were excluded pairwise.

6.3.3.4 Concentrations of HbA1C were significantly different between those who adhered to the AHA guidelines for physical activity and those who did not

Independent samples t-tests were used to detect differences in levels of metabolic markers between those who met the AHA guidelines for physical activity and those who did not. Assessment of the study group showed that levels of HbA1C were significantly higher in participants who did not adhere to the AHA guidelines for physical activity in comparison to participants who met the guidelines (mean levels of HbA1C; those who met the guidelines: 34.1, those who did not meet the guidelines: 37.9 (mmol/mol); $p = 0.026$, $t = -2.28$). There was no significant difference in fasting glucose levels and levels of insulin between the two groups.

Figure 6.6.3.13 Levels of HbA1C were significantly higher in patients with psoriasis who did not meet the AHA guidelines for physical activity (n=117)

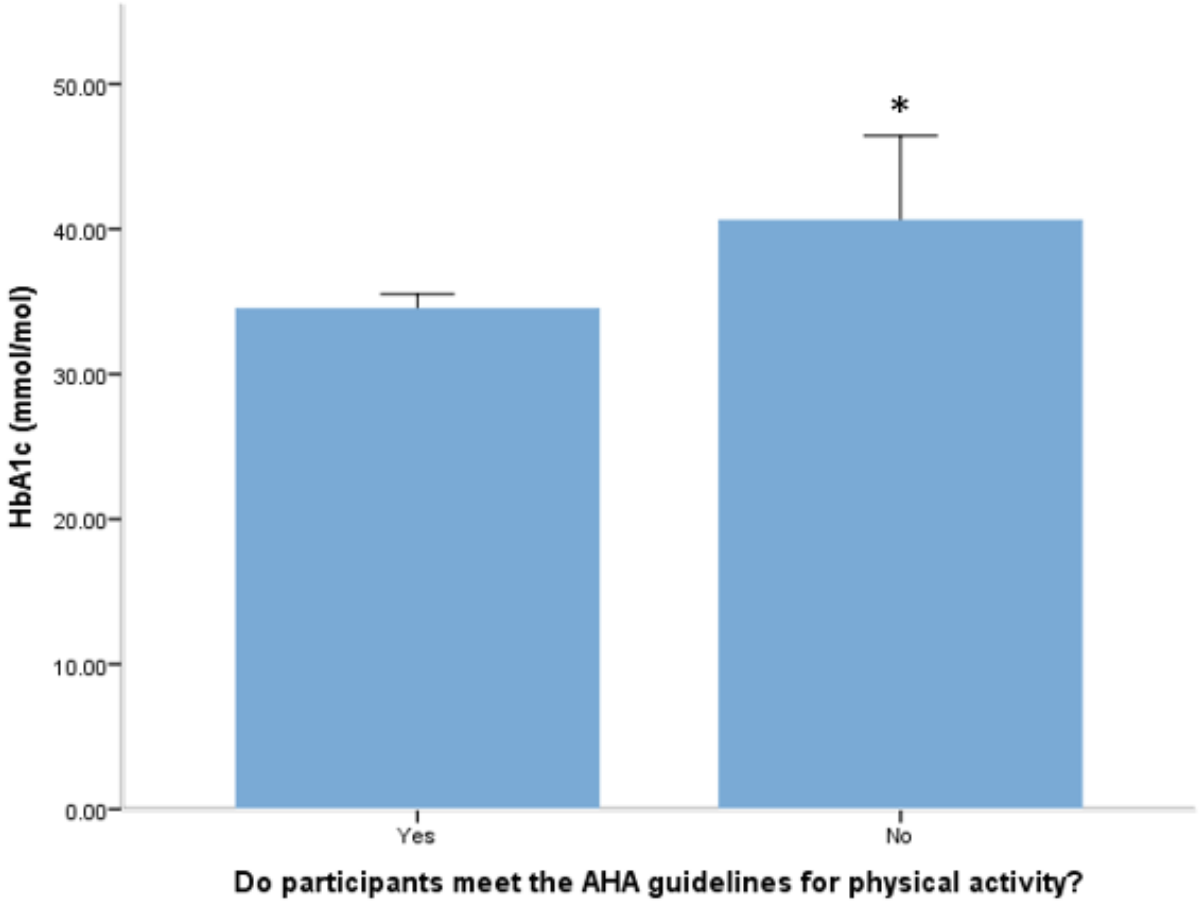


The bar chart above highlights the difference in HbA1C levels between patients with psoriasis who are sufficiently active in order to meet the AHA guidelines for physical activity and those who do not participate in enough physical activity to meet these guidelines. The participants who did not meet the guidelines for physical activity had significantly higher levels of HbA1C (p = 0.026).

Examination of gender differences revealed that male participants who did not meet the AHA guidelines had significantly higher levels of HbA1C than those who did meet the guidelines (mean levels of HbA1C; those who met the guidelines: 34.5, those who

did not meet the guidelines: 40.6 (mmol/mol); p = 0.049, t = -2.06). However, no significant differences in fasting glucose or insulin levels were found between the two groups.

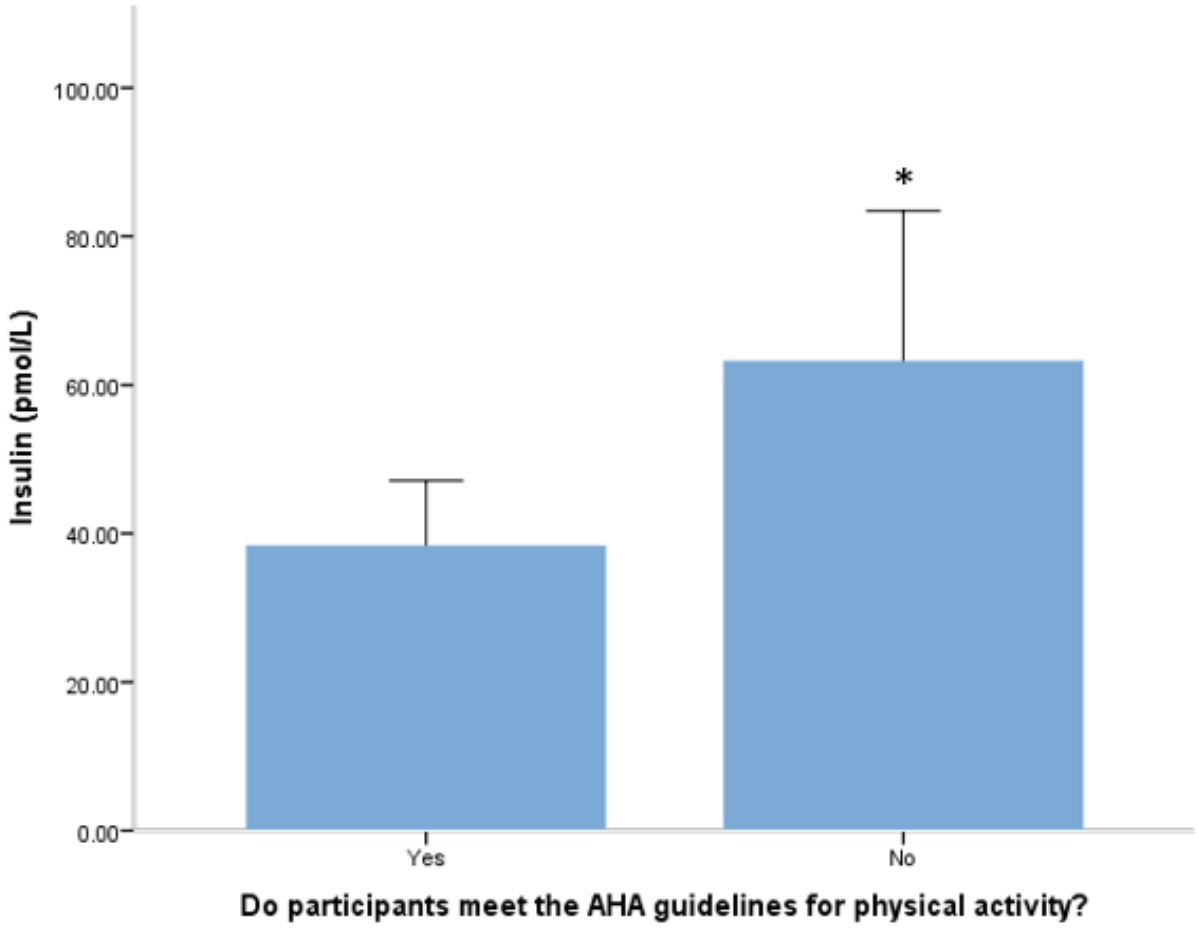
Figure 6.6.3.14 Levels of HbA1C were significantly higher in males with psoriasis who did not meet the AHA guidelines for physical activity (n=66)



The bar chart highlights the difference in HbA1C levels between males, with psoriasis, who are sufficiently active in order to meet the AHA guidelines for physical activity and those who do not participate in enough physical activity to meet these guidelines. Male participants who did not meet the guidelines for physical activity had significantly higher levels of HbA1C (P = 0.049).

The assessment of female participants highlighted a significant difference in insulin levels between the two groups. It was observed that those who did not meet the AHA guidelines for physical activity had significantly higher levels of insulin in their blood compared to those who adhered to the guidelines (mean levels of HbA1C; those who met the guidelines: 38.3, those who did not meet the guidelines: 63.1 (mmol/mol); $p = 0.032$, $t = -0.244$). However, no significant differences in fasting glucose or HbA1C levels were observed between the groups.

Figure 6.6.3.15 Insulin levels were significantly higher in females with psoriasis who did not meet the AHA guidelines for physical activity (n=51)



The bar chart highlights the difference in insulin levels between females, with psoriasis, who are sufficiently active in order to meet the AHA guidelines for physical activity and those who do not participate in enough physical activity to meet these guidelines. Female participants who did not meet the guidelines for physical activity had significantly higher levels of insulin (P = 0.032).

Tables 6.6.3.1, 6.6.3.2 and 6.6.3.3 summarise the mean levels of metabolic markers in those who adhere to the AHA guidelines and those who do not.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Table 6.6.3.1 Mean insulin levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of insulin (pmol/L)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	54.9 (9.2)	64 (13.8)	**38.3 (4.4)***
AHA guidelines for physical activity not met	80 (11.2)	98.4 (20.2)	**63.1 (10.2)***

*Results are presented as means with standard error of the mean in brackets. Significant results are highlighted in bold. *P < 0.05*

Table 6.6.3.2 Mean fasting glucose levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of fasting glucose (mmol/L)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	4.9 (0.06)	5 (0.1)	4.8 (0.1)
AHA guidelines for physical activity not met	5.5 (0.3)	6 (0.5)	5.1 (0.2)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.3.3 Mean HbA1C levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of HbA1C (mmol/mol)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	**34.1 (0.4)***	**34.5 (0.5)***	33.4 (0.6)
AHA guidelines for physical activity not met	**37.9 (1.6)***	**40.6 (2.9)***	35 (1.0)

*Results are presented as means with standard error of the mean in brackets. Significant results are highlighted in bold. *P < 0.05*

6.3.3.5 Levels of metabolic markers were not significantly correlated with PASI in patients with psoriasis

Spearman correlations were performed in order to assess the relationship between metabolic markers and PASI. Previous work has shown that insulin and fasting glucose levels are elevated in patients with psoriasis (Karadag et al., 2010, Fitzgerald et al., 2014). It has also been recognised that insulin levels are significantly associated with PASI (Uysal et al., 2014).

These analyses address the following specific hypothesis: there will be a significant correlation between psoriasis severity (PASI) and levels of metabolic markers.

The results from these analyses revealed no significant correaltions between levels of metabolic markers and PASI in patients with psoriasis.

These results remained unchanged following sensitivity analyses excluding patients with psoriatic arthritis.

6.6.4 Adipokines: leptin, adiponectin and resistin

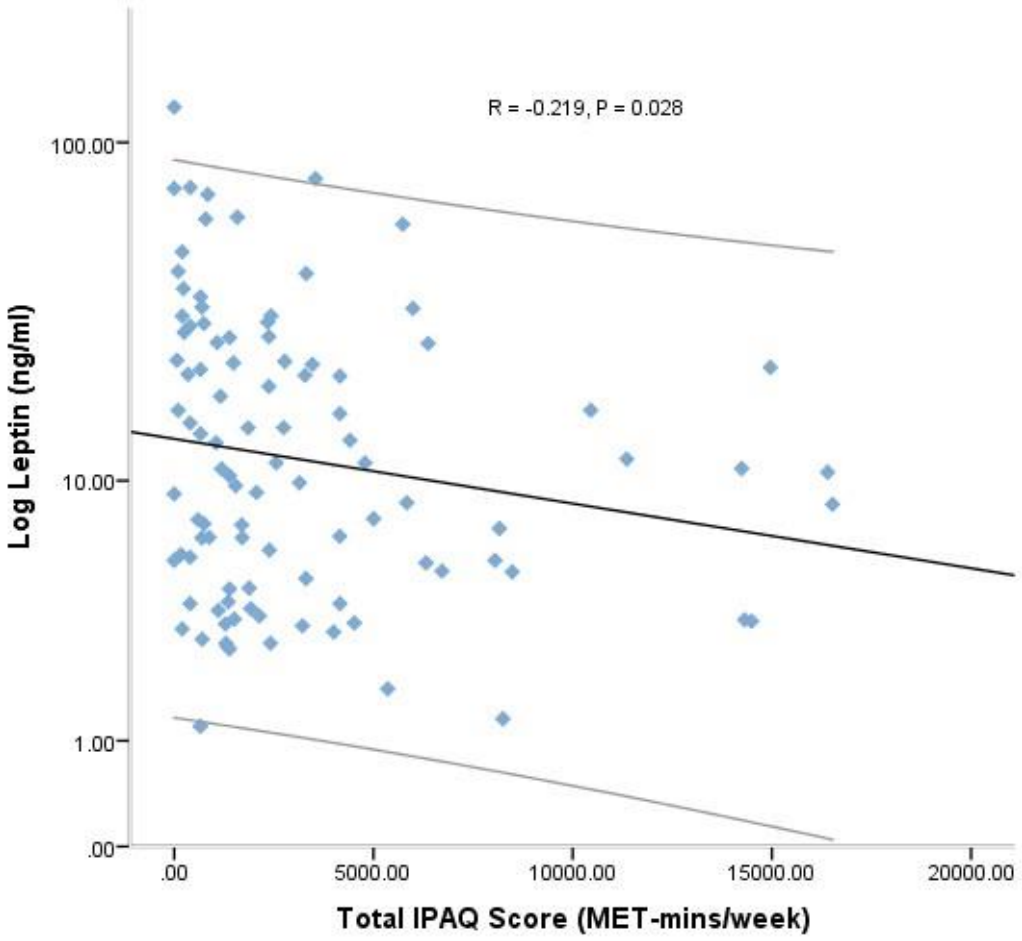
6.6.4.1 Leptin was significantly, inversely correlated with physical activity in people with psoriasis, whilst adiponectin was correlated with physical activity

Previous literature has consistently reported that physical activity reduces the levels of both leptin (Gomez-Merino et al., 2002, Donahue et al., 1999) and resistin (Kadoglou et al., 2007). However, although it is believed that adiponectin levels may be increased by physical activity, the findings reported in the literature are inconsistent (Emken et al., 2010, Simpson and Singh, 2008). It has been proposed that high levels of adiponectin may be beneficial as it promotes insulin sensitivity and has anti-inflammatory properties (Kadowaki et al., 2006).

These analyses address the following specific hypotheses: concentrations of leptin and resistin will be significantly, inversely correlated with self-reported levels of physical activity. However, adiponectin concentration will be significantly correlated with activity levels.

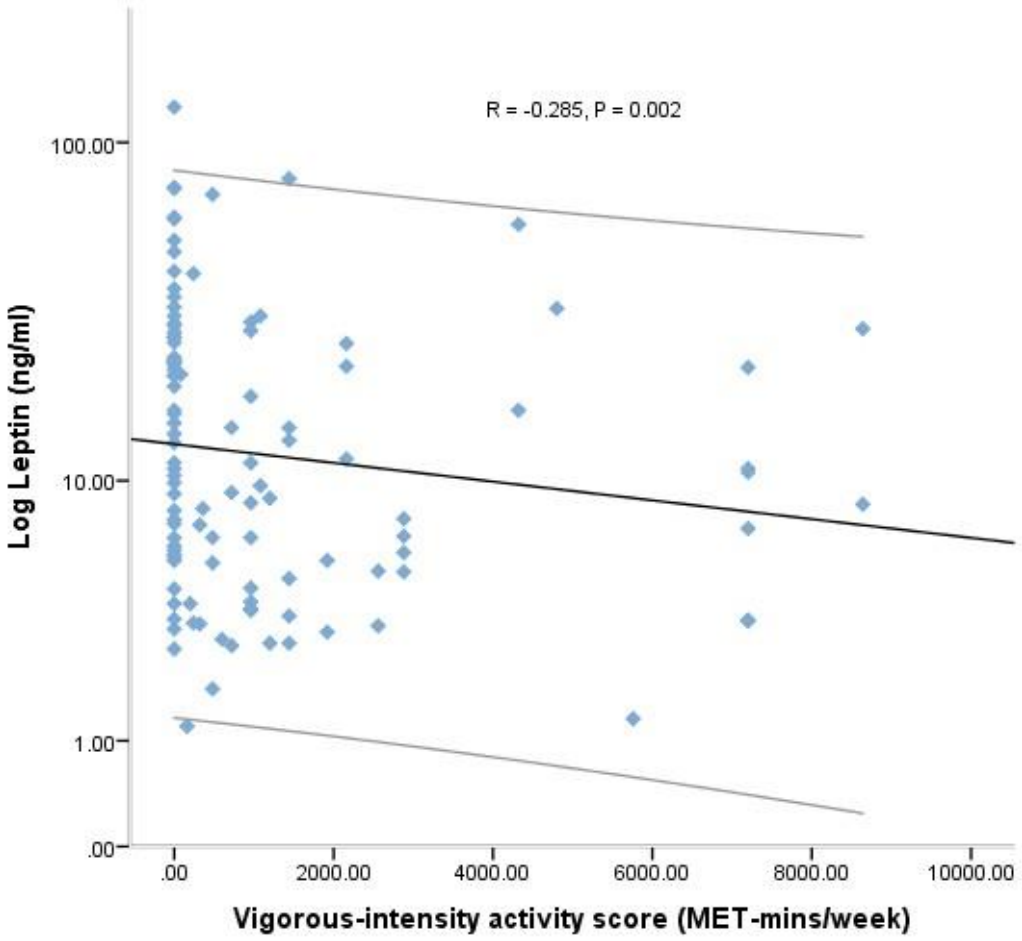
Assessment of the study group revealed significant negative correlations between leptin and total IPAQ scores ($r = -0.219$, $p = 0.028$) and leptin and vigorous-intensity physical activity ($r = -0.285$, $p = 0.002$). Therefore, as activity scores increased, leptin concentrations decreased. It was also found that adiponectin was significantly correlated with total IPAQ scores ($r = 0.233$, $p = 0.019$). No significant correlations were observed between resistin and physical activity. Indeed, it is important to take into consideration the potential confounding effects of psoriatic arthritis. The presence of this condition may impede a patient's ability to exercise.

Figure 6.6.4.1 Physical activity was significantly, inversely correlated with leptin concentration in patients with psoriasis (n=100)



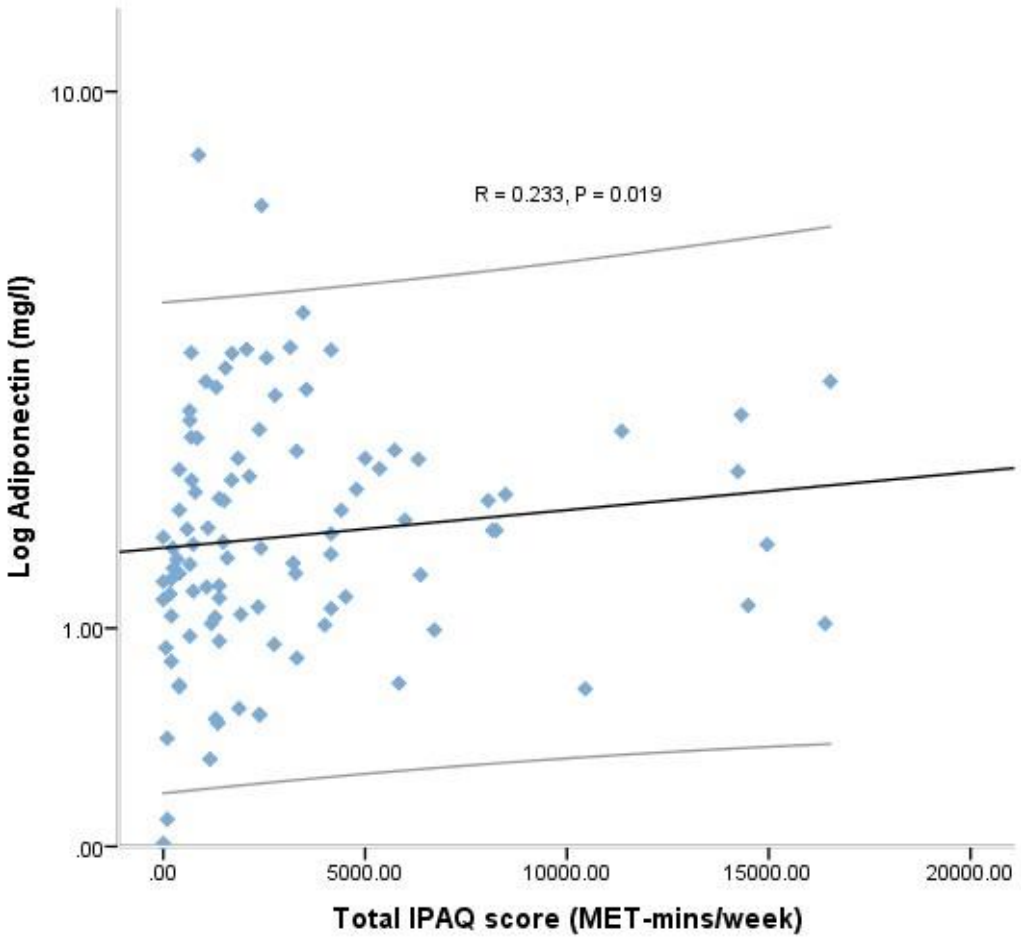
The scatter plot above depicts the correlation between physical activity and leptin concentration in patients with psoriasis. The significant negative correlation indicates that leptin levels reduce with increasing physical activity. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 14.5%; missing cases were excluded pairwise.

Figure 6.6.4.2 Vigorous-intensity physical activity was significantly correlated with leptin concentration in patients with psoriasis (n=111)



The scatter plot above presents the correlation between vigorous-intensity physical activity and leptin concentration in patients with psoriasis. The significant negative correlation indicates that leptin levels reduce with increasing vigorous-intensity activity. The correlation between these two variables was stronger than that of leptin and total IPAQ scores, indicating that vigorous-intensity activity is potentially more effective in reducing leptin levels. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 5.1%; missing cases were excluded pairwise.

Figure 6.6.4.3 Physical activity was significantly correlated with adiponectin concentration in patients with psoriasis (n=100)



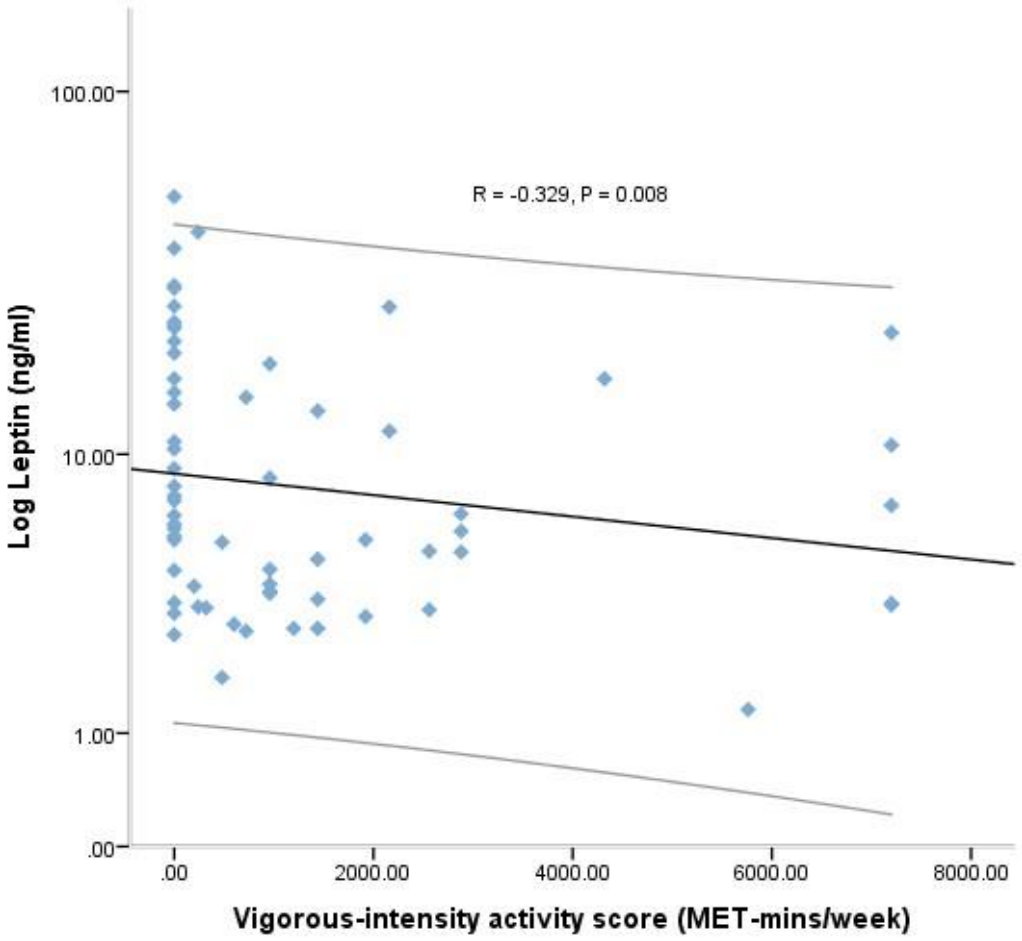
The scatter plot above depicts the correlation between physical activity and adiponectin concentration in patients with psoriasis. The significant negative correlation indicates that adiponectin levels elevate with increasing physical activity. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 14.5%; missing cases were excluded pairwise.

Subsequently, study group 3 was split into males and females and reassessed. In males, a significant inverse correlation was highlighted between leptin and vigorous-intensity physical activity ($r = -0.329$, $p = 0.008$). Therefore, as vigorous-intensity physical activity scores increased, leptin concentrations decreased.

It was also found in males that adiponectin was significantly correlated with total IPAQ scores ($r = 0.254$, $p = 0.05$). A significant correlation between resistin and walking scores was also detected amongst male participants ($r = 0.262$, $p = 0.043$). These findings were not significant following sensitivity analyses which excluded patients with psoriatic arthritis.

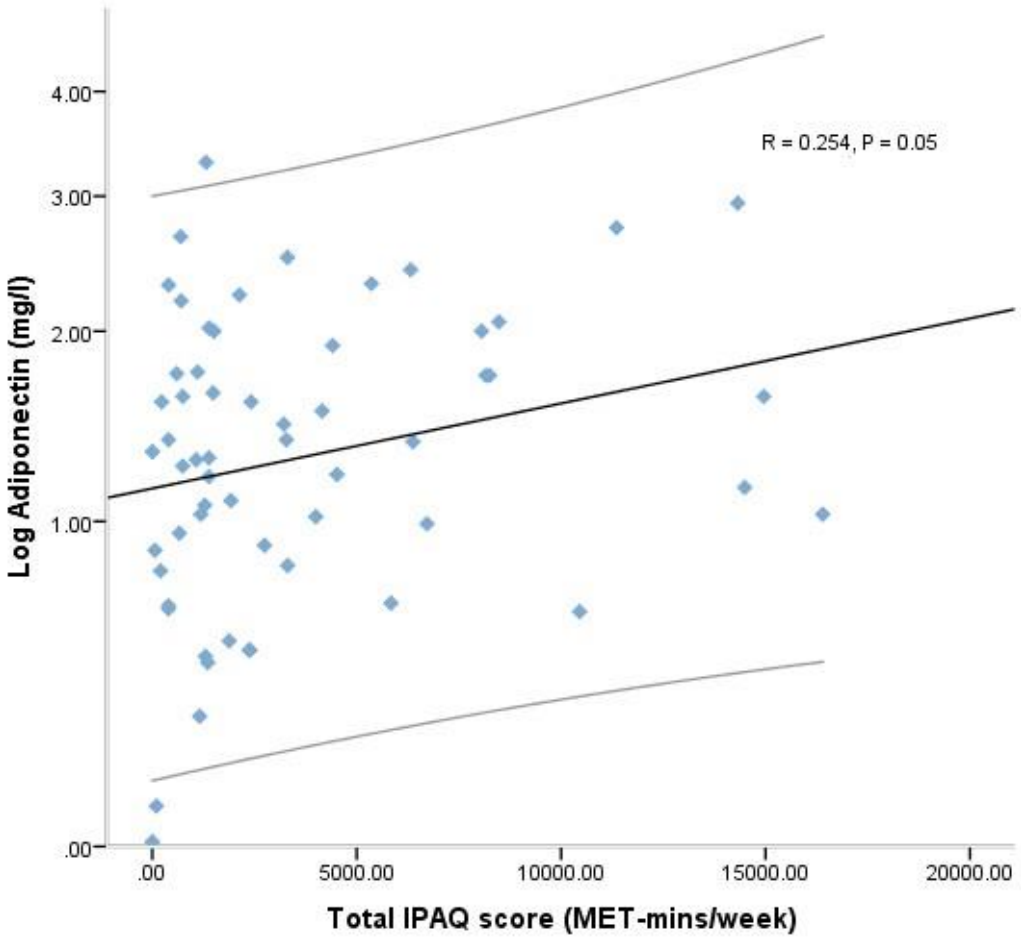
However, the sensitivity analyses did reveal a significant correlation between adiponectin and vigorous-intensity physical activity in males with psoriasis ($r = 0.32$, $p = 0.004$).

Figure 6.6.4.4 Vigorous-intensity physical activity was significantly, inversely correlated with leptin concentration in males with psoriasis (n=64)



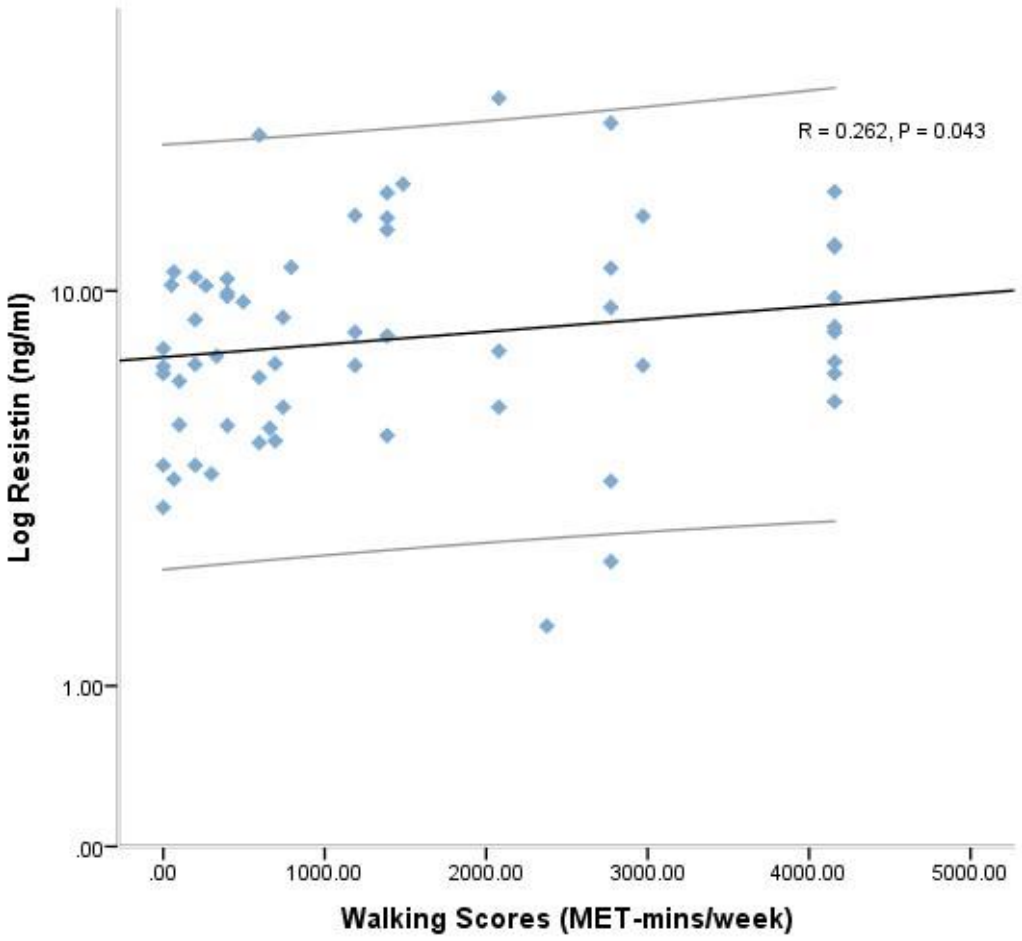
The scatter plot above presents the correlation between vigorous-intensity physical activity and leptin concentration in males with psoriasis. The significant inverse correlation indicates that leptin levels reduce with increasing vigorous-intensity activity. A similar relationship was observed between these variables upon examination of study group 3 as a whole cohort. However, from this scatter plot it is evident that this correlation is stronger within the male population of study group 3. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 3%; missing cases were excluded pairwise.

Figure 6.6.4.5 Physical activity was significantly correlated with adiponectin concentration in males with psoriasis (n=59)



The scatter plot above highlights the correlation between physical activity and adiponectin concentration in males with psoriasis. The significant negative correlation indicates that adiponectin levels elevate with increasing physical activity. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Adiponectin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 10.6%; missing cases were excluded pairwise.

Figure 6.6.4.6 Mild-intensity physical activity (walking) was significantly correlated with resistin levels in males with psoriasis (n=60)

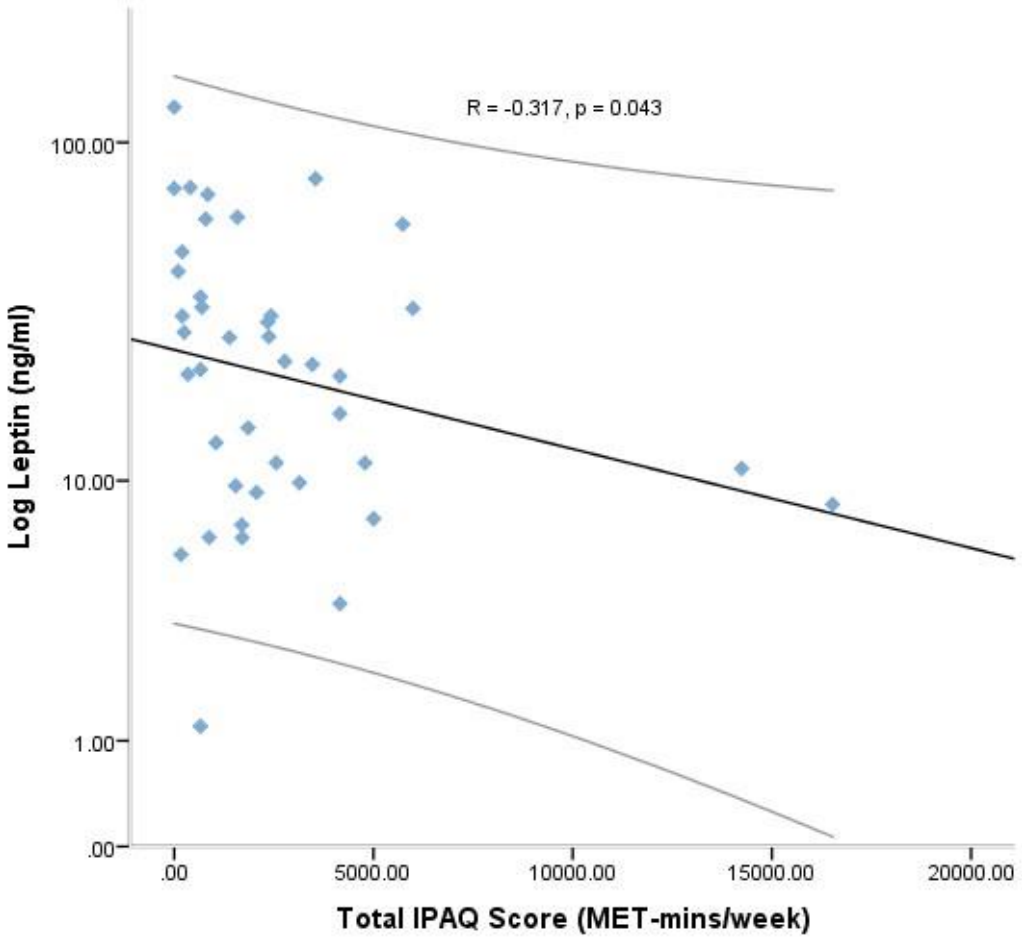


The scatter plot above depicts the correlation between mild-intensity physical activity (walking) and resistin concentration in males with psoriasis. The significant positive correlation indicates that resistin levels increase with increasing physical activity. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Resistin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 9.1%; missing cases were excluded pairwise.

In females, significant inverse correlations were observed between leptin and total IPAQ scores ($r = -0.317$, $p = 0.043$) and leptin and walking scores ($r = -0.333$, $p = 0.029$). Therefore, as activity scores increased, leptin concentrations decreased. However, these findings were not significant following sensitivity analyses which excluded patients with psoriatic arthritis (all other findings remained unchanged after excluding for these patients).

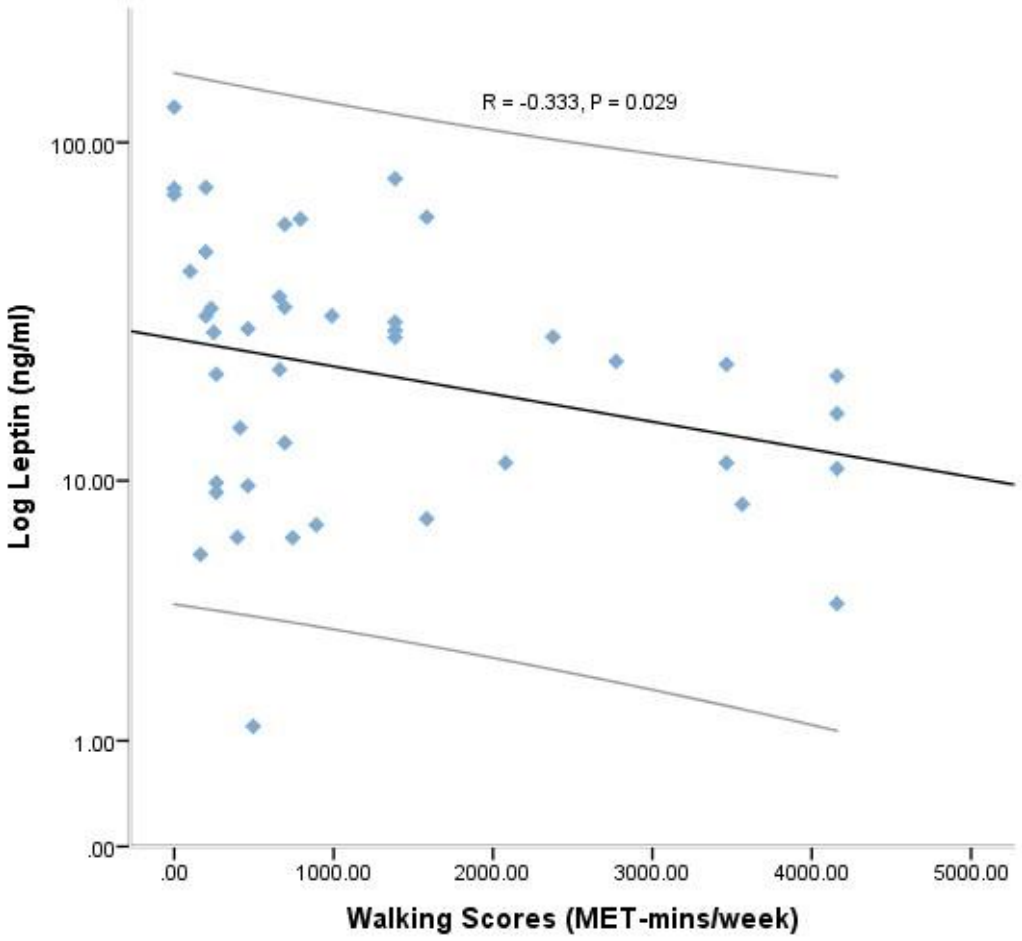
Additionally, it was found that, in females, adiponectin was significantly correlated with total IPAQ scores ($r = 0.404$, $p = 0.009$). There were no significant correlations observed between physical activity scores and resistin in females.

Figure 6.6.4.7 Physical activity was significantly, inversely correlated with leptin concentration in females with psoriasis (n=41)



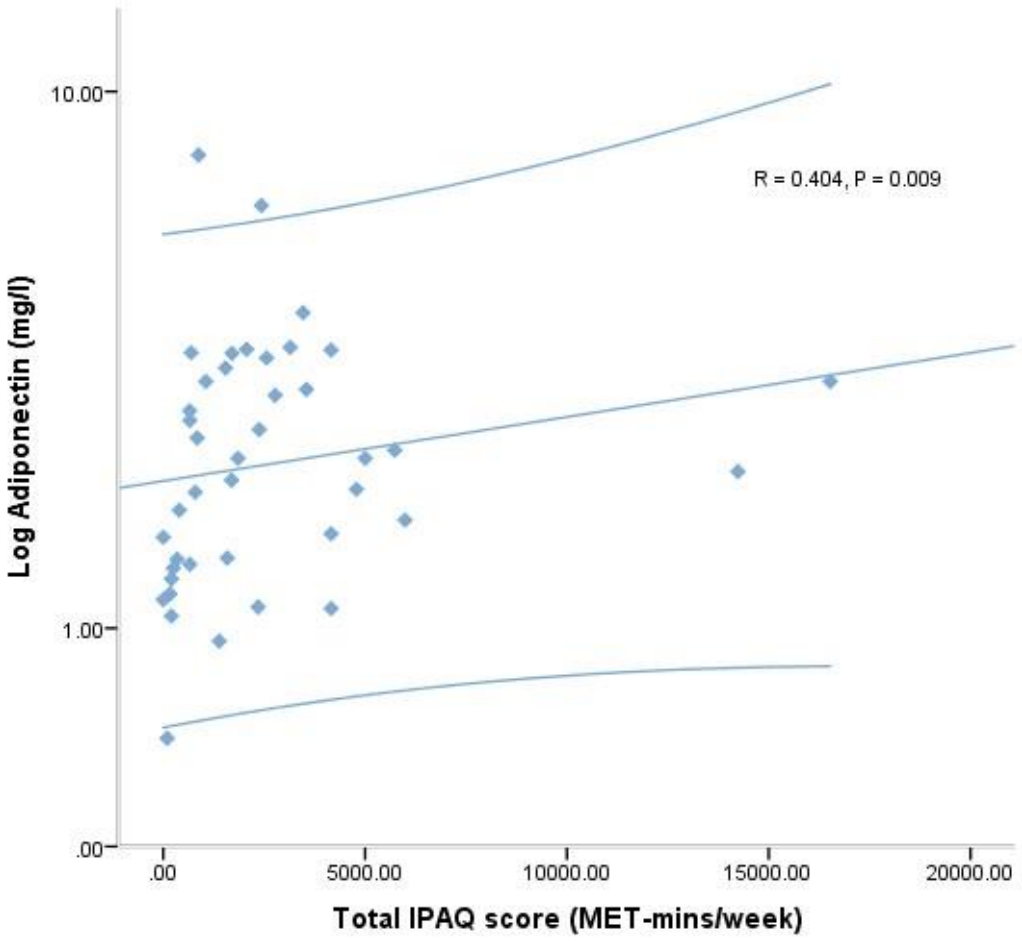
The scatter plot highlights the correlation between physical activity and leptin concentration in females with psoriasis. The significant negative correlation indicates that leptin levels elevate with increasing physical activity. This correlation is stronger than that observed in study group 3 as a whole. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 19.6%; missing cases were excluded pairwise.

Figure 6.6.4.8 Mild-intensity physical activity (walking) was significantly, inversely correlated with leptin levels in females with psoriasis (n=43)



The scatter plot presents the correlation between mild-intensity physical activity (walking) and levels of leptin in females with psoriasis. The significant inverse correlation indicates that leptin levels deplete as physical activity increases. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 15.7%; missing cases were excluded pairwise.

Figure 6.6.4.9 Physical activity was significantly correlated with adiponectin concentration in females with psoriasis (n=41)



The scatter plot presents the correlation between physical activity and levels of adiponectin in females with psoriasis. The significant positive correlation indicates that adiponectin levels increase as physical activity increases. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Adiponectin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 19.6%; missing cases were excluded pairwise.

6.6.4.2 Leptin was significantly correlated with PWV in males with psoriasis

Previous studies have reported that increased levels of leptin and resistin are positively associated with arterial stiffness and endothelial dysfunction (Lee et al., 2014, Singhal et al., 2002, Fang et al., 2013). In contrast, an inverse relationship between adiponectin and arterial stiffness has been documented (Mahmud and Feely, 2005a, Youn et al., 2013)

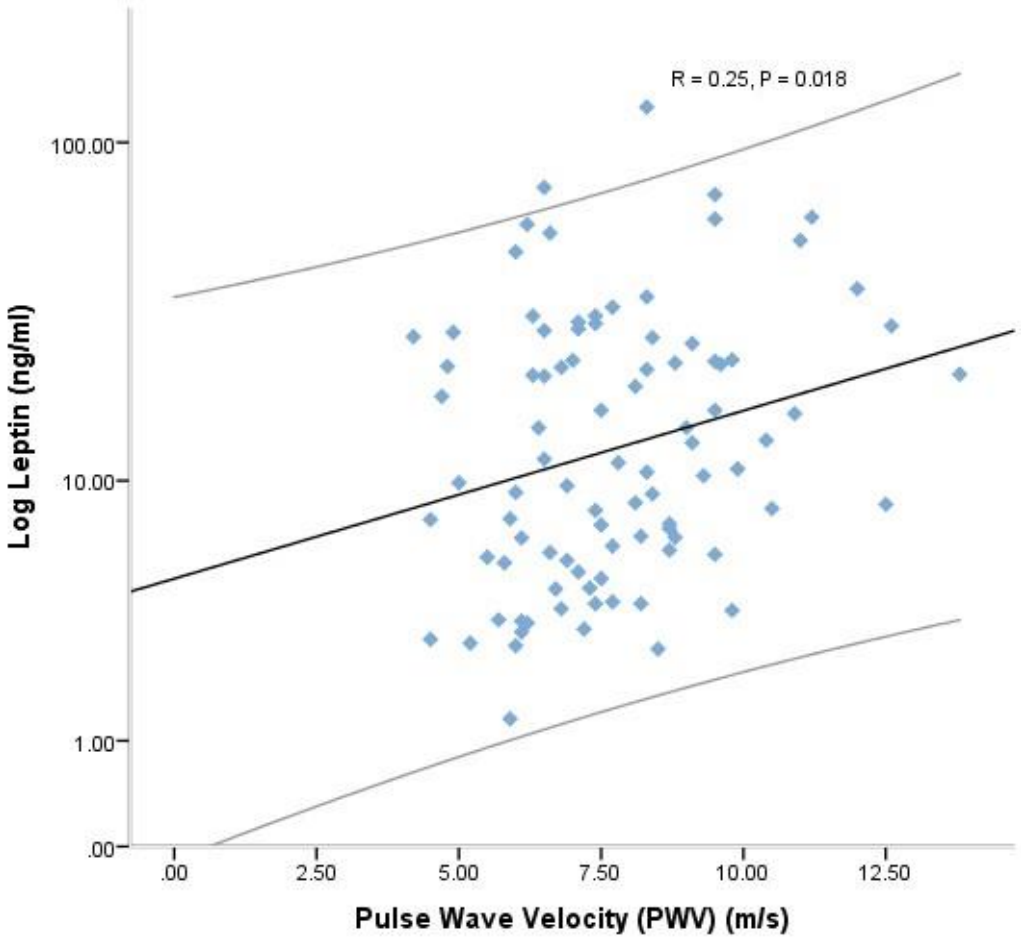
These analyses address the following specific hypotheses: there will be a significant correlation between arterial stiffness (PWV) and both leptin and resistin. However, there will be a significant inverse correlation between PWV and adiponectin concentration.

Assessment of the study group indicated no significant correlations between adiponectin and PWV and resistin and PWV. However, a significant correlation was observed in between leptin and arterial stiffness ($r = 0.25$, $p = 0.018$).

Examination of gender differences highlighted a significant correlation between leptin and arterial stiffness in males ($r = 0.509$, $P = <0.001$). There were no significant correlations between PWV and any of the metabolic markers in females.

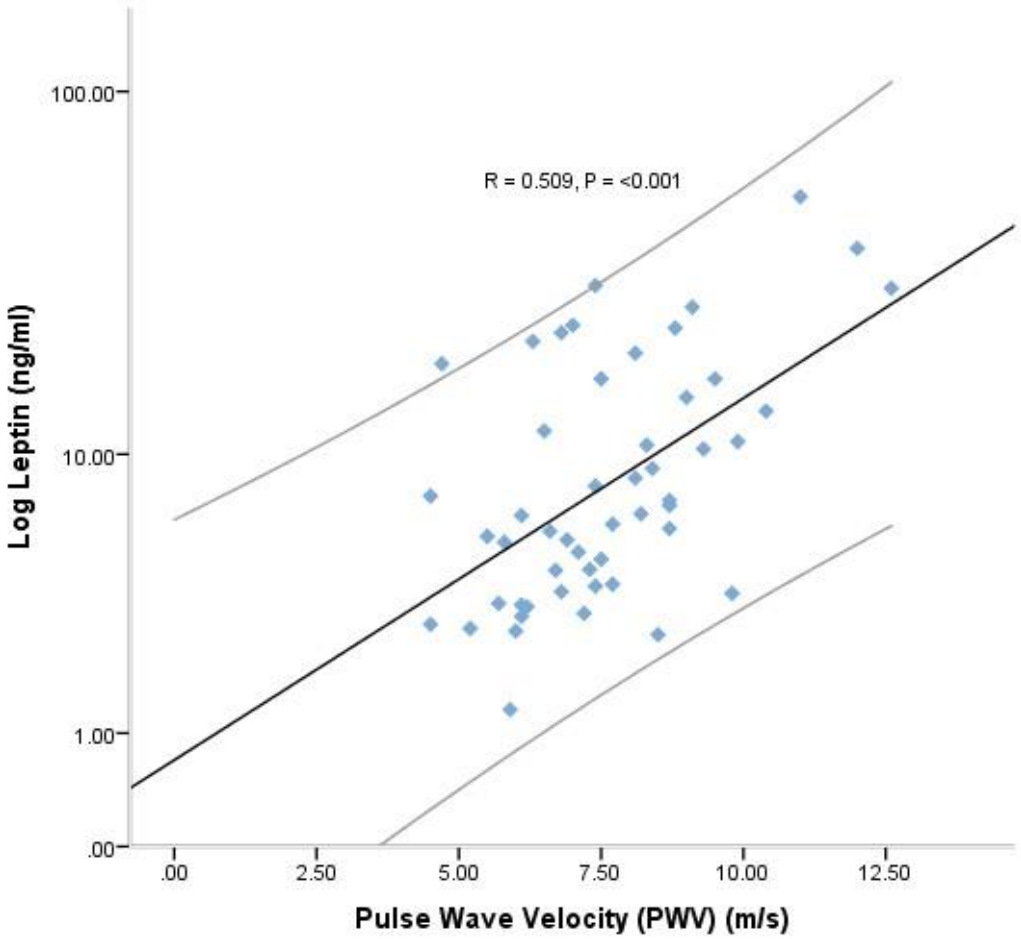
These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Figure 6.6.4.10 Pulse wave velocity was significantly correlated with leptin concentration in patients with psoriasis (n=90)



The scatter plot highlights the correlation between PWV and levels of leptin in patients with psoriasis. The significant positive correlation indicates that PWV values increase with increasing concentrations of leptin. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 23.1%; missing cases were excluded pairwise.

Figure 6.6.4.11 Pulse wave velocity was significantly correlated with leptin concentration in males with psoriasis (n=51)



The scatter plot presents the correlation between PWV and levels of leptin in males with psoriasis. The significant positive correlation indicates that leptin levels increase as physical activity increases. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 22.7%; missing cases were excluded pairwise.

6.6.4.3 There was no significant correlation between DRA and concentration of adipokines in people with psoriasis

These analyses address the following specific hypotheses: there will be significant inverse correlations between cardiorespiratory fitness (DRA) and both leptin and resistin. However, there will be a significant correlation between DRA and adiponectin concentration.

Assessment of the study group revealed no relationship between the chosen adipokines (leptin, resistin and adiponectin) and DRA. Examination of gender differences also found no significant correlations between adipokines concentrations and DRA.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

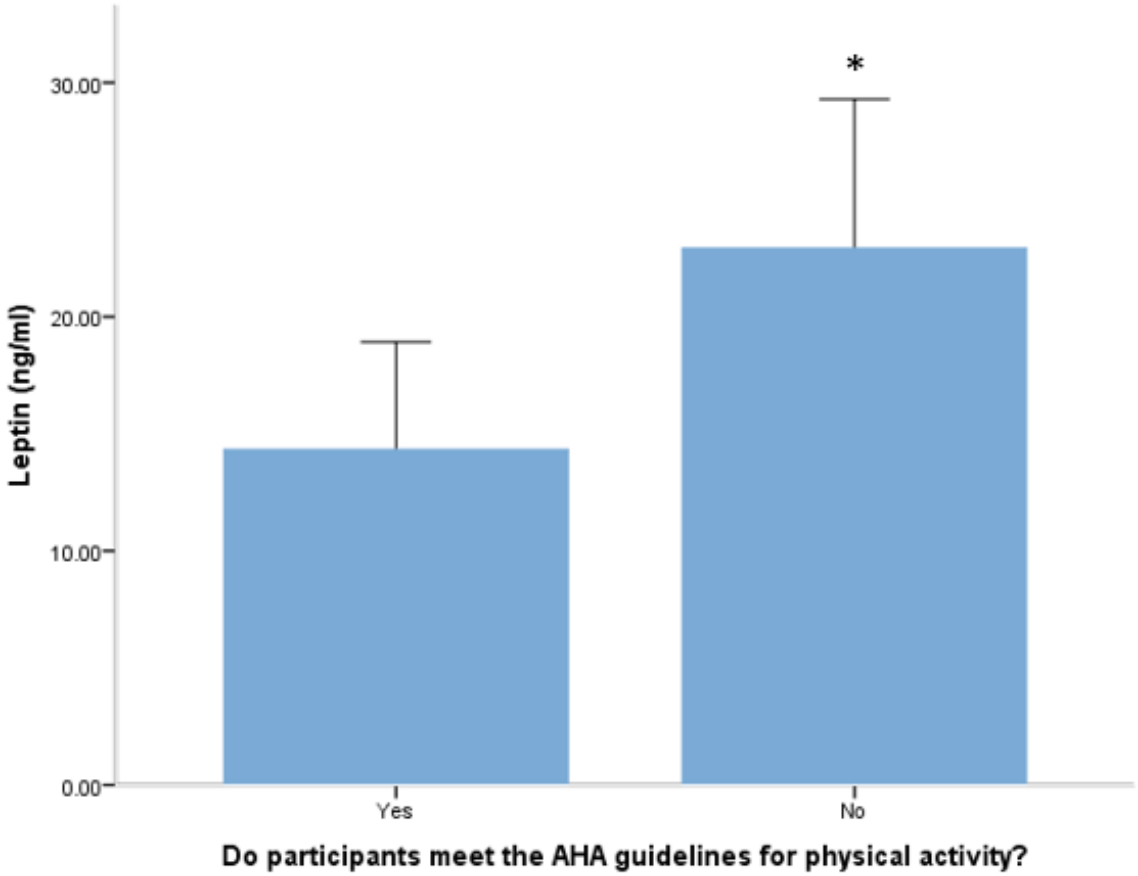
6.6.4.4 Leptin concentrations were significantly lower in those who adhered to the AHA guidelines for physical activity compared to those who did not

Independent samples t-tests were used to detect differences in levels of adipokines between those who met the AHA guidelines for physical activity and those who did not.

Assessment of the study group showed that those who did not meet the AHA guidelines for physical activity had significantly higher levels of leptin than those who met the guidelines (mean levels of leptin; those who met the guidelines: 14.3, those who did not meet the guidelines: 22.9 (ng/ml); $p = 0.03$, $t = -2.202$). There was no significant difference in levels of adiponectin or resistin between the two groups.

Examination of gender differences revealed no significant differences in adipokines levels between those who adhered to the AHA guidelines and those who did not.

Figure 6.6.4.12 Leptin levels were significantly higher in patients with psoriasis who did not meet the AHA guidelines for physical activity (n=117)



The bar chart highlights the difference in leptin levels between patients with psoriasis, who are sufficiently active in order to meet the AHA guidelines for physical activity and those who do not participate in enough physical activity to meet these guidelines. Participants who did not meet the guidelines for physical activity had significantly higher levels of leptin (P = 0.03).

Tables 6.6.4.1, 6.6.4.2 and 6.6.4.3 summarise the mean levels of leptin, resistin and adiponectin in those who adhere to the AHA guidelines and those who do not.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Table 6.6.4.1 Mean leptin levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of leptin (ng/ml)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	**14.3 (2.3)***	9.8 (1.9)	23 (5.2)
AHA guidelines for physical activity not met	**22.9 (3.2)***	13.2 (1.9)	33.4 (5.6)

*Results are presented as means with standard error of the mean in brackets. Significant results are highlighted in bold. *P < 0.05*

Table 6.6.4.2 Mean resistin levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of resistin (ng/ml)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	9.2 (0.6)	9.5 (0.8)	8.5 (0.9)
AHA guidelines for physical activity not met	8.8 (0.6)	7.9 (0.9)	9.8 (0.8)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.4.3 Mean adiponectin levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of adiponectin (mg/l)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	2 (0.2)	1.5 (0.1)	2.9 (0.3)
AHA guidelines for physical activity not met	1.8 (0.2)	1.2 (0.1)	2.4 (0.3)

Results are presented as means with standard error of the mean in brackets.

6.6.4.5 Adiponectin levels were significantly inversely correlated with PASI

Spearman correlations were performed in order to assess the relationship between adipokines and PASI. Previous work has shown that both leptin and resistin are positively associated with PASI (Boehncke et al., 2007a, Cerman et al., 2008). It has also been observed that adiponectin levels are inversely associated with disease activity (Shibata et al., 2011).

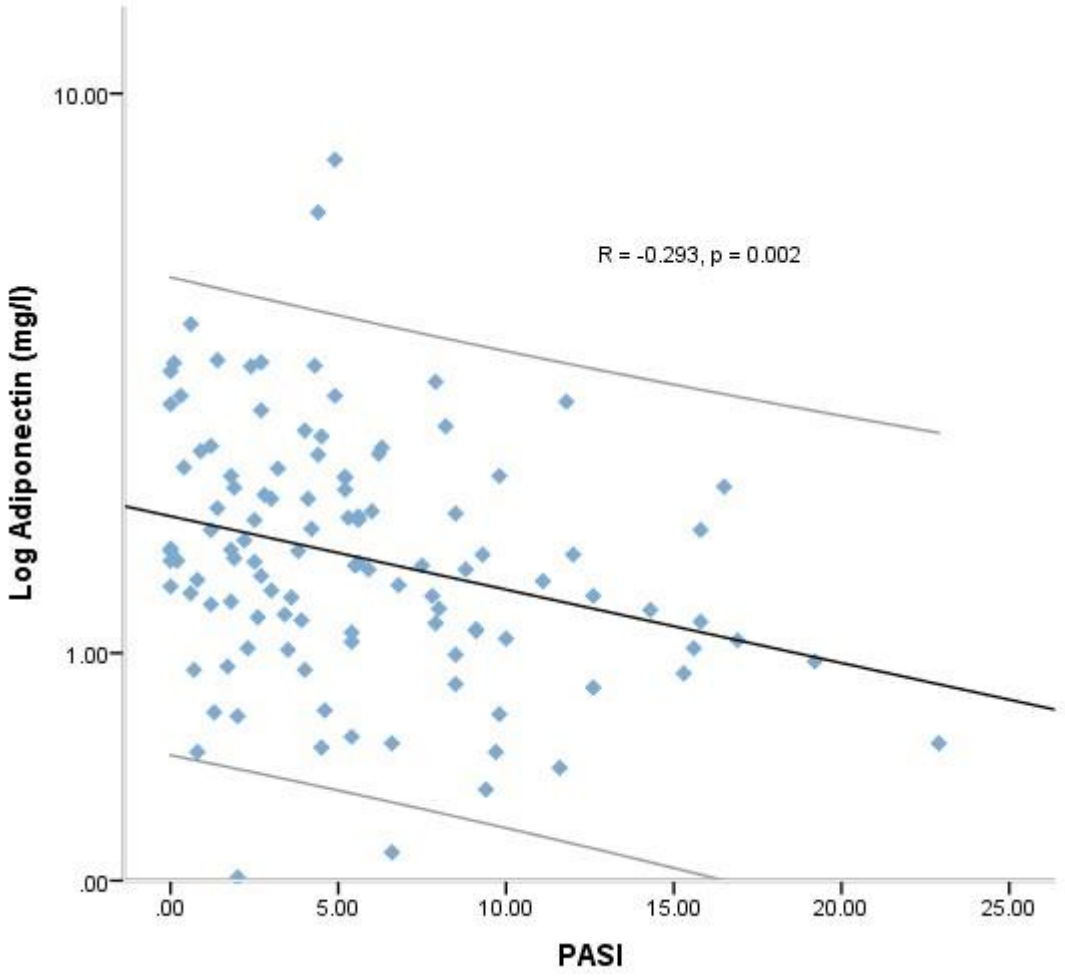
These analyses address the following specific hypotheses: there will be significant correlations between psoriasis severity (assessed using the PASI) and both leptin and resistin. In contrast, there will be a significant, inverse correlation between PASI and adiponectin concentration.

Assessment of the study group revealed that levels of adiponectin were significantly, inversely correlated with PASI ($r = -0.293$, $p = 0.002$). However, both leptin and resistin showed no significant correlation with PASI.

Examination of gender differences revealed no significant correlations between these adipokines and PASI in male participants. Similarly, the examination of female participants also showed no significant correlations between the adipokines and PASI.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Figure 6.6.4.5 Levels of adiponectin were significantly inversely correlated with PASI in patients with psoriasis (n=112)



The scatter plot highlights the correlation between PASI and levels of adiponectin in patients with psoriasis. The significant inverse correlation indicates that PASI values increase with increasing levels of adiponectin. The black line on the graph represents the fit line and the grey lines on each side of the fit line represent confidence intervals. Leptin concentration is presented on a log scale (base-10) to aid visualisation of the range of data on the plot. Missing data: 4.3%; missing cases were excluded pairwise.

6.6.5 Circulating lipids: cholesterol, HDL-cholesterol, LDL-cholesterol, total- HDL cholesterol ratio and triglycerides

For the purpose of the analyses presented in this section participants with diabetes or those currently on lipid lowering medication were excluded.

6.6.5.1 Total-HDL cholesterol ratio and triglyceride concentrations were significantly, negatively correlated with physical activity in females with psoriasis

It is well-established that physical activity enhances lipid lipoprotein profiles by reducing levels of (total) cholesterol, LDL-cholesterol and triglycerides and increasing levels of HDL-cholesterol (Huttunen et al., 1979, Haskell et al., 1980, Warburton et al., 2006). However, the extent of the beneficial effects of physical activity may depend on the type, frequency and duration of physical activity (Warburton et al., 2006).

These analyses address the following specific hypothesis: physical activity will be significantly, negatively correlated with levels of total cholesterol, LDL-cholesterol, triglycerides and total-HDL cholesterol ratio. In contrast, physical activity will be significantly correlated with levels of HDL-cholesterol.

Assessment of the study group revealed a significant inverse correlation between total cholesterol levels and total IPAQ scores ($r = -0.218$, $p = 0.045$). Therefore, as levels of physical activity decrease, cholesterol levels increase. LDL-cholesterol, HDL-cholesterol, total-HDL cholesterol ratio and triglyceride levels showed no significant correlations with self-reported levels of physical activity. Sensitivity analyses which excluded patients with psoriatic arthritis, revealed an additional significant inverse correlation between triglyceride levels and vigorous-intensity

physical activity (r = -0.278, p = 0.023). All other findings remained unchanged following the sensitivity analyses.

Examination of gender differences revealed, a significant inverse correlation between triglyceride levels and vigorous-intensity physical activity (r = -0.286, p = 0.032), in male participants. Sensitivity analyses which excluded male patients with psoriatic arthritis, revealed an additional significant inverse correlation between total-HDL cholesterol ratio and vigorous-intensity physical activity (r = -0.328, p = 0.045). All other findings remained unchanged following the sensitivity analyses.

In females, significant negative correlations were identified between the following variables: total-HDL cholesterol ratio and total IPAQ scores (r = -0.408, p = 0.013), triglycerides and total IPAQ scores (r = -0.529, p = 0.001) and triglycerides and walking scores (r = -0.416, p = 0.009). Sensitivity analyses which excluded female patients with psoriatic arthritis, revealed an additional significant inverse correlation between total-HDL cholesterol ratio and total IPAQ scores (r = -0.397, p = 0.049). All other findings remained unchanged following the sensitivity analyses.

6.6.5.2 Total cholesterol, LDL-cholesterol, total-HDL cholesterol ratio and triglyceride concentration were all significantly correlated with PWV, while HDL-cholesterol was significantly inversely correlated with PWV in males with psoriasis

It is well-established that serum lipids are associated with arterial stiffness, particularly levels of LDL-cholesterol which are known to be associated with arterial stiffness. In contrast, HDL-cholesterol levels are inversely correlated with arterial stiffness (Wang et al., 2011).

These analyses address the following specific hypothesis: there will be significant, correlations between arterial stiffness (PWV) and the following lipid variables: total

cholesterol, LDL-cholesterol, triglycerides, total-HDL cholesterol ratio. In contrast, there will be a significant inverse correlation between HDL-cholesterol and PWV.

Assessment of the study group revealed significant correlations between the following variables: total cholesterol and PWV ($r = 0.403$, $p<0.001$), LDL-cholesterol and PWV ($r = 0.434$, $p<0.001$), total-HDL cholesterol ratio and PWV ($r = 0.362$, $p = 0.001$) and triglycerides and PWV ($r = 0.296$, $p = 0.007$). However, there was no significant correlation observed between HDL-cholesterol and PWV.

Individual assessment of the male participants revealed significant correlations between the following variables: total cholesterol and PWV ($r = 0.403$, $p<0.001$), LDL-cholesterol and PWV ($r = 0.381$, $p = 0.01$), total-HDL cholesterol ratio and PWV ($r = 0.5$, $p<0.001$) and triglycerides and PWV ($r = 0.487$, $p = 0.001$). A significant inverse correlation was also observed between HDL-cholesterol and PWV ($r = -0.295$, $p = 0.047$). Sensitivity analyses which excluded male patients with psoriatic arthritis revealed no significant correlations between levels of HDL-cholesterol and PWV and levels of LDL-cholesterol and PWV. However, all other results remained unchanged after excluding participants with psoriatic arthritis.

Individual examination of the female participants revealed significant correlations between the following variables: total cholesterol and PWV ($r = 0.559$, $p<0.001$), LDL-cholesterol and PWV ($r = 0.552$, $p<0.001$) and total-HDL cholesterol ratio and PWV ($r = 0.459$, $p = 0.005$).

6.6.5.3 Total cholesterol and DRA were significantly inversely correlated in people with psoriasis

Physical activity is known to reduce levels of total cholesterol, LDL-cholesterol and triglycerides and increase levels of HDL-cholesterol (Huttunen et al., 1979, Warburton

et al., 2006). These analyses address the following specific hypothesis: there will be significant, inverse correlations between cardiorespiratory fitness (DRA) and the following lipid variables: total cholesterol, LDL-cholesterol, triglycerides, total-HDL cholesterol ratio. In contrast, there will be a significant positive correlation between HDL-cholesterol and DRA.

Assessment of the study group revealed a significant inverse correlation between total-cholesterol and DRA in people with psoriasis ($r = -0.224$, $p = 0.041$).

Examination of gender differences revealed no significant correlations between circulatory lipids and DRA. However, sensitivity analyses which excluded patients with psoriatic arthritis, revealed a significant inverse correlation between total-HDL cholesterol ratio and DRA ($r = -0.397$, $p = 0.049$) in females. However, all other results remained unchanged after excluding participants with psoriatic arthritis.

6.6.5.4 There were no significant differences in levels of circulatory lipids between those who adhered to the AHA guidelines for physical activity and those who did not

Independent samples t-tests were used to detect differences in levels of circulatory fats between those who met the AHA guidelines for physical activity and those who did not.

The results from these analyses revealed no significant differences in the levels of circulatory fats between those who adhered to the AHA guidelines and those who did not.

Tables 6.6.5.1, 6.6.5.2, 6.6.5.3, 6.6.5.4 and 6.6.5.5 summarise the mean levels of circulatory lipids in those who adhere to the AHA guidelines and those who do not.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Table 6.6.5.1 Mean cholesterol levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of cholesterol (mmol/L)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	5.2 (0.2)	5.2 (0.2)	5 (0.3)
AHA guidelines for physical activity not met	5.3 (0.1)	5.4 (0.2)	5.2 (0.2)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.5.2 Mean HDL-cholesterol levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of HDL-cholesterol (mmol/L)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	1.5 (0.06)	1.4 (0.07)	1.7 (0.1)
AHA guidelines for physical activity not met	1.4 (0.05)	1.2 (0.06)	1.6 (0.06)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.5.3 Mean LDL-cholesterol levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of LDL-cholesterol (mmol/L)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	3.1 (0.2)	3.2 (0.2)	2.9 (0.3)
AHA guidelines for physical activity not met	3.2 (0.1)	3.3 (0.2)	3 (0.1)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.5.4 Mean total-HDL cholesterol ratio for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Mean total-HDL cholesterol ratio		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	3.8 (0.2)	4.2 (0.2)	3.2 (0.3)
AHA guidelines for physical activity not met	4 (0.2)	4.6 (0.3)	3.3 (0.2)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.5.5 Mean triglyceride levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of triglycerides (mmol/L)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	1.3 (0.1)	1.5 (0.2)	0.9 (0.1)
AHA guidelines for physical activity not met	1.6 (0.1)	1.8 (0.2)	1.3 (0.2)

Results are presented as means with standard error of the mean in brackets.

6.6.5.5 LDL-cholesterol was significantly inversely correlated with PASI in females with psoriasis

Spearman correlations were performed in order to assess the relationship between lipid profile and PASI. Previous findings have been inconsistent in determining the relationship between lipid profile and disease severity in patients with psoriasis (Azfar and Gelfand, 2008).

These analyses address the following specific hypothesis: there will be significant, correlations between psoriasis severity (as measured by the PASI) and the following lipid variables: total cholesterol, LDL-cholesterol, triglycerides, total-HDL cholesterol ratio. In contrast, there will be a significant inverse correlation between HDL-cholesterol levels and the PASI.

Assessment of the study group revealed no significant correlations between the lipid parameters and PASI.

Subsequent examination of male participants also revealed no significant correlations between lipid profile and PASI.

The examination of female participants highlighted a significant correlation between LDL-cholesterol and PASI (r = -0.306, p = 0.046). However, no other significant correlations were observed between the remaining lipid measures and PASI.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

6.6.6 Inflammatory cytokines: TNF-α, IL-6 and hs-CRP

6.6.6.1 hs-CRP was significantly, inversely correlated with physical activity in people with psoriasis

Previous research has shown that regular physical activity can significantly lower circulating CRP and inflammatory cytokine concentrations (Goldhammer et al., 2005, Okita et al., 2004, Toft et al., 2002). A study by Reuben et al reported lower plasma concentrations of IL-6 and TNF-α in physically active individuals compared to age and sex-matched inactive groups (Reuben et al., 2003). Various studies have also observed an inverse relationship between physical activity and CRP levels (Pischon et al., 2003, Aronson et al., 2004). In patients with psoriasis these markers of systemic inflammation are elevated (Dowlatshahi et al., 2013). These analyses address the following specific hypothesis: there will be significant, inverse correlations between concentrations of inflammatory markers and self-reported levels of physical activity.

Assessment of the study group revealed a significant negative correlation between hs-CRP and total IPAQ scores (r = -0.294, p = 0.003). Both TNF-α and IL-6 showed no significant correlation with physical activity. Sensitivity analyses which excluded patients with psoriatic arthritis, revealed significant inverse correlations between the following variables: hs-CRP and mild-intensity physical activity (r = -0.269, p = 0.022), hs-CRP and moderate-intensity physical activity (r = -0.245, p = 0.035) and hs-CRP

and vigorous-intensity physical activity (r = -0.266, p = 0.018). However, all other findings remained unchanged following the exclusion of patients with psoriatic arthritis.

Examination of gender differences identified a significant correlation between IL-6 and walking scores (r = 0.282, p = 0.029), in male participants. Sensitivity analyses which excluded male patients with psoriatic arthritis, revealed significant inverse correlations between the following variables: hs-CRP and total IPAQ scores (r = -0.339, p = 0.033), hs-CRP and moderate-intensity physical activity (r = -0.344, p = 0.024) and hs-CRP and vigorous-intensity physical activity (r = -0.353, p = 0.019). However, all other results remained unchanged after excluding participants with psoriatic arthritis.

In females, significant negative correlations were identified between the following variables: hs-CRP and total IPAQ scores (r = -0.517, p = 0.001) and hs-CRP and walking scores (r = -0.424, p = 0.005).

6.6.6.2 hs-CRP was significantly correlated with PWV in males with psoriasis

Previous studies have highlighted a relationship between inflammatory markers and arterial stiffness in both healthy individuals and those with a CVD risk (Mahmud and Feely, 2005b, Vlachopoulos et al., 2005). Levels of hs-CRP, IL-6 and TNF-α have been shown to be correlated with arterial stiffness (Mahmud and Feely, 2005b).

These analyses aim to address the following specific hypothesis: there will be significant correlations between arterial stiffness (PWV) and levels of inflammatory markers.

Assessment of the study group revealed no significant correlations between the inflammatory markers and PWV.

However, examination of gender differences revealed a significant correlation between hs-CRP and PWV ($r = 0.299$, $p = 0.033$) in male participants.

There were no significant correlations identified in female participants.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

6.6.6.3 There was no significant correlation between concentrations of inflammatory markers and DRA in people with psoriasis

Taking into account the anti-inflammatory effects of physical activity (Petersen and Pedersen, 2005), these analyses address the following specific hypothesis: there will be significant, inverse correlations between cardiorespiratory fitness (DRA) and levels of inflammatory markers (hs-CRP, TNF-α and IL-6).

Assessment of the study group identified no significant correlations between DRA and levels of inflammatory markers.

Similarly, examination of gender differences also revealed no significant correlations between DRA and levels of inflammatory markers.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

6.6.6.4 There were no significant differences in levels of inflammatory markers between those who adhered to the AHA guidelines for physical activity and those who did not

Independent samples t-tests were used to detect differences in levels of hs-CRP, TNF-α and IL-6 between those who met the AHA guidelines for physical activity and those who did not.

The results from these analyses revealed no significant differences in the levels of circulatory fats between those who adhered to the AHA guidelines and those who did not.

Tables 6.6.6.1, 6.6.6.2 and 6.6.6.3 show the mean concentrations of inflammatory markers for those who adhere to the AHA guidelines for physical activity and those who do not.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

Table 6.6.6.1 Mean hs-CRP levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of hs-CRP (mg/l)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	3.4 (0.7)	4 (1.1)	2.3 (0.5)
AHA guidelines for physical activity not met	2.8 (0.4)	2.6 (0.4)	3 (0.7)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.6.2 Mean TNF-α levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of TNF-α (pg/ml)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	57.1 (25.2)	28.4 (11.4)	112.9 (70.2)
AHA guidelines for physical activity not met	54.7 (23.3)	68 (35.2)	40.8 (30.9)

Results are presented as means with standard error of the mean in brackets.

Table 6.6.6.3 Mean IL-6 levels for participants who adhere to the AHA guidelines for physical activity and those who do not.

	Levels of IL-6 (pg/ml)		
	Study group 3 (n=117)	Males (n=66)	Females (n=51)
AHA guidelines for physical activity met	3.6 (1.7)	3.9 (2.5)	3 (1.5)
AHA guidelines for physical activity not met	2.3 (1.1)	2.9 (1.9)	1.5 (0.7)

Results are presented as means with standard error of the mean in brackets.

6.6.6.5 Inflammatory biomarkers show no significant correlations with PASI

Spearman correlations were performed in order to assess the relationship between inflammatory biomarkers and PASI. The findings in the literature are inconsistent, some studies have indicated a significant correlation between hs-CRP (Beygi et al., 2014) and TNF-α (Mussi et al., 1997) and IL-6. However, various studies have reported no relationship between Il-6 and disease severity (Takahashi et al., 2010, Arican et al., 2005).

These analyses address the following specific hypothesis: there will be significant, positive correlations between psoriasis severity (as measured by the PASI) and levels of inflammatory markers).

Assessment of the study group revealed no significant correlations between inflammatory biomarker and PASI.

Similarly, examination of gender differences also highlighted no significant correlations between levels of inflammatory markers and PASI.

These results remained unchanged following sensitivity analyses which excluded patients with psoriatic arthritis.

6.6.7 Hierarchical regression models

This section will present the results obtained from hierarchical regression analyses. In order to quantify the contribution made by psoriasis factors, co-morbidities and exercise profile on each biomarker a hierarahial regression analysis wes performed. The biomarkers which were found to correlate with physical activity were selected for this regression analysis. A hierarchical regression model was constructed for each biomarker, with the biomarker as the dependent variable. The independent variables which were entered into each model included demographic factors, psoriasis severity measures and physical activity. The independent variables were entered in sequence in order to determine whether physical activity scores are still able to explain some of the remaining variance in the biomarker concentrations when statistically controlling for the other independent variables.

In order to qualtify the contribution made by the biomarlers to CVD risk, biomarkers which were found to correlate with PWV were also selected for regression analysis, with PWV as the dependent variable. The independent variables which were entered

into this model included demographic factors, psoriasis severity measures, physical activity scores and biomarker concentrations (only those biomarkers which were found to correlate with PWV in previous analyses). A separate analysis and regression model was constructed with DRA as the dependent variable.

Sensitivity analyses were carried out in order in order to assess the impact of outliers on the regression models presented in this section. The results of these analyses revealed that the outliers did not affect the results of the regressions. Therefore, the outlying data points were kept in the models. The IPAQ variable (total IPAQ scores) was transformed using the logarithm function in order to normalise the distribution of this variable.

6.6.7.1 Levels of sE-selectin in people with psoriasis were not significantly influenced by demographic variables, psoriasis severity measures or physical activity

A four stage hierarchical multiple regression was conducted with sE-selectin as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI was entered in block two, psoriasis severity measures in block three (modified version of the SPI-i and PASI) and total IPAQ scores in block four of the regression. BMI, PASI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis). Disease duration was excluded from the regression as there was no significant correlation observed between this variable and sE-selectin. Psoriatic arthritis was also excluded, as the sensitivity analyses that was carried out previously (see section 6.6.2.1) showed that excluding for people with

psoriatic arthritis had no impact on the findings. The results from this multiple regression analysis are presented in table 6.6.7.1.

Table 6.6.7.1 Summary of hierarchical regression analysis for variables predicting sE-selectin concentration (n=107).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			0.062	0.061	0.062	0.061
Age	0.113	0.279				
Sex	**-0.208**	**0.049**				
Block 2:			0.069	0.099	0.007	0.405
Age	0.1	0.344				
Sex	-0.204	0.053				
BMI	0.088	0.405				
Block 3:			0.083	0.187	0.014	0.53
Age	0.116	0.285				
Sex	-0.172	0.119				
BMI	0.093	0.385				
Modified-SPI-i	0.111	0.310				
PASI	-0.061	0.573				
Block 4:			0.104	0.151	0.021	0.166
Age	0.101	0.353				
Sex	-0.198	0.076				
BMI	0.069	0.519				
Modified-SPI-i	0.084	0.445				
PASI	-0.072	0.503				
Total IPAQ scores	-0.151	0.166				

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: sE-selectin. Statistically significant values are highlighted in bold. Missing data: 8.5%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 6.2% of the variation in sE-selectin levels. However, the R^2 change was not significant. Introducing BMI in block 2 explained an additional 0.7%, however, this change in R^2 was not significant. Adding the psoriasis severity measures (PASI and modified SPI-i) explained a further 1.4% of the variation in sE-selectin levels, however, the change in R^2 was also not significant. Finally, the addition of physical activity to the regression model explained 2.1% of the variation in sE-selectin levels. The R^2 change, upon the addition of physical activity, was not significant. When all six independent variables

were included in the final stage of the regression model it was revealed that none of the variables were significant predictors of sE-selectin levels. Together the six independent variables accounted for 10.4% of the variance in sE-selectin levels.

6.6.7.2 BMI was found to be a significant predictor of insulin levels in people with psoriasis

A four stage hierarchical multiple regression was conducted with insulin as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI and psoriatic arthritis were entered in block two, the modified version of the SPI-i in block three and total IPAQ scores in block four of the regression. Psoriatic arthritis was added together in the same block as BMI, as it was found, in a sensitivity analysis, that adding them into the model separately did not alter the overall fit or significance of the model and it also did not affect the beta values (and whether they were significant or not) of the variables themselves). These variables were treated in the same way for all other hierarchical regression models presented in this chapter.

BMI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis).

For the purpose of this model, participants with diabetes and those on lipid lowering medication were excluded from the analysis.

Disease duration and PASI were excluded from the regression as there was no significant correlation observed between these variables and insulin. The results from this multiple regression analysis are presented in table 6.6.7.2.

Table 6.6.7.2 Summary of hierarchical regression analysis for variables predicting insulin levels (n=88).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			0.02	0.491	0.02	0.491
Age	0.039	0.739				
Sex	-0.128	0.28				
Block 2:			**0.204**	**0.003**	**0.185**	**0.001**
Age	-0.019	0.867				
Sex	-0.111	0.309				
BMI	**0.434**	**<0.001**				
Psoriatic arthritis	0.001	0.995				
Block 3:			**0.21**	**0.005**	0.006	0.475
Age	-0.03	0.792				
Sex	-0.116	0.291				
BMI	**0.422**	**<0.001**				
Psoriatic arthritis	-0.022	0.848				
Modified-SPI-i	-0.083	0.475				
			0.217	**0.009**	0.006	0.461
Block 4:	-0.034	0.766				
Age	-0.123	0.264				
Sex	**0.411**	**<0.001**				
BMI	-0.037	0.749				
Psoriatic arthritis	0.08	0.493				
Modified-SPI-i	-0.083	0.461				
Total IPAQ scores						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: insulin. Statistically significant values are highlighted in bold. Participants with diabetes and those on lipid lowering medication were excluded from this model (12.8%). Missing data: 13.7%. .

Block 1 of the hierarchical regression revealed that age and sex accounted for 20% of the variation in insulin levels. However, the contribution of these variables was not significant. Introducing BMI and psoriatic arthritis in block 2 explained an additional 18.5% of the variance in levels of insulin and this change in R^2 was significant (p = 0.001). Adding the modified SPI-i variable explained a further 0.6% of the variance in levels of insulin. However, this change in R^2 was not significant. Finally, the addition of physical activity to the regression model explained 0.6% of the variation in levels

of insulin. The R^2 change, upon the addition of physical activity, was not significant. Together the six independent variables accounted for 21.7% of the variance in levels of insulin. This model, as a whole, was found to be significant ($F = 3.13$, $p = 0.009$). BMI was the only variable making a significant contribution to the regression model ($\beta = 0.411$, $p<0.001$).

6.6.7.3 BMI and age were significant predictors of fasting glucose levels in patients with psoriasis

A four stage hierarchical multiple regression was conducted with fasting glucose as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI and psoriatic arthritis were entered in block two, psoriasis severity measures in block three (modified version of the SPI-i and PASI) and total IPAQ scores in block four of the regression. BMI, PASI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis).

For the purpose of this model, participants with diabetes and those on lipid lowering medication were excluded from the analysis.

Disease duration was excluded from the regression as there was no significant correlation observed between this variable and fasting glucose levels. The results from this multiple regression analysis are presented in table 6.6.7.3.

Table 6.6.7.3 Summary of hierarchical regression analysis for variables predicting fasting glucose levels (n=96).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.08**	**0.037**	**0.08**	**0.037**
Age	0.186	0.093				
Sex	-0.187	0.091				
			0.141	**0.019**	0.061	0.072
Block 2:	0.184	0.101				
Age	-0.179	0.099				
Sex	**0.221**	**0.042**				
BMI	-0.121	0.27				
Psoriatic arthritis			**0.19**	**0.013**	0.05	0.108
Block 3:	**0.224**	**0.046**				
Age	-0.124	0.265				
Sex	**0.254**	**0.019**				
BMI	-0.06	0.589				
Psoriatic arthritis	-0.204	0.075				
Modified-SPI-i	0.144	0.191				
PASI			**0.192**	**0.022**	0.002	0.676
	0.22	**0.05**				
Block 4:	-0.131	0.247				
Age	**0.248**	**0.025**				
Sex	-0.07	0.544				
BMI	-0.204	0.075				
Psoriatic arthritis	0.135	0.231				
Modified-SPI-i	-0.046	0.676				
PASI						
Total IPAQ scores						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: fasting glucose. Statistically significant values are highlighted in bold. Participants with diabetes and those on lipid lowering medication were excluded from this model (12.8%). Missing data: 5.9%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 8% of the variation in fasting glucose levels and this change in R^2 was found to be significant ($p = 0.037$). Introducing BMI and psoriatic arthritis in block 2 explained an additional 6.1% of variance in fasting glucose levels. This change in R^2 was not significant. Adding the psoriasis severity measures (PASI and modified SPI-i) explained a further

5% of variance in levels of fasting glucose, although this change in R^2 was not

significant. Finally, the addition of physical activity to the regression model explained 0.2% of the variation in levels of fasting glucose. However, the change in R^2 was not significant. Together the seven independent variables accounted for 19.2% of the variance in levels of fasting glucose. This model as a whole was significant (F = 2.51, p = 0.022). The variables which made a significant contribution to the regression model, in order of importance were BMI (β = 0.248, p = 0.025) and age (β = 0.22, p = 0.05).

6.6.7.4 Sex and BMI were significant predictors of leptin levels in people with psoriasis

A four stage hierarchical multiple regression was conducted with leptin as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI and psoriatic arthritis were entered in block two, the modified SPI-i in block three and total IPAQ scores in block four of the regression. BMI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis). Disease duration and PASI were excluded from the regression as there were no significant correlations observed between these variables and leptin. The results from this multiple regression analysis are presented in table 6.6.7.4.

Table 6.6.7.4 Summary of hierarchical regression analysis for variables predicting levels of leptin (n=112).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.203**	**<0.001**	**0.203**	**<0.001**
Age	0.084	0.372				
Sex	**0.453**	**<0.001**				
			0.621	**<0.001**	**0.418**	**<0.001**
Block 2:	-0.001	0.994				
Age	**0.478**	**<0.001**				
Sex	**0.656**	**<0.001**				
BMI	-0.07	0.294				
Psoriatic arthritis			**0.621**	**<0.001**	0	0.921
Block 3:	-0.001	0.983				
Age	**0.478**	**<0.001**				
Sex	**0.655**	**<0.001**				
BMI	-0.071	0.301				
Psoriatic arthritis	0.007	0.921				
Modified-SPI-i			**0.627**	**<0.001**	0.006	0.218
Block 4:	-0.008	0.909				
Age	**0.467**	**<0.001**				
Sex	**0.642**	**<0.001**				
BMI	-0.08	0.245				
Psoriatic arthritis	0.002	0.981				
Modified-SPI-i	-0.084	0.218				
Total IPAQ scores						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: leptin. Statistically significant values are highlighted in bold. Missing data: 4.3%.

Block 1 of the hierarchical regression revealed that age and sex contributed significantly to the regression model ($p<0.001$) and accounted for 20.3% of the variation in leptin levels. Introducing BMI and psoriatic arthritis in block 2 explained an additional 41.8% of variance in leptin levels. This change in R^2 was found to be significant ($p<0.001$). Adding the modified SPI-i variable in block 3 had no effect on the R^2 value. Finally, the addition of physical activity to the regression model explained 0.6% of the variation in levels of leptin. However, the change in R^2 was not

significant. Together the six independent variables accounted for 62.7% of the variance in levels of leptin. This model, as a whole, was found to be significant ($F = 24.99$, $p<0.001$). The variables which made a significant contribution to the regression model, in order of importance, include: BMI ($\beta = 0.642$, $p = <0.001$) and sex ($\beta = 0.467$, $p = <0.001$).

6.6.7.5 Sex, BMI and age were significant predictors of adiponectin levels in patients with psoriasis

A four stage hierarchical multiple regression was conducted with adiponectin as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI and psoriatic arthritis were entered in block two, psoriasis severity measures in block three (modified version of the SPI-i and PASI) and total IPAQ scores in block four of the regression. BMI, PASI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis). Disease duration was excluded from the regression as there was no significant correlation observed between this variable and adiponectin levels. The results from this multiple regression analysis are presented in table 6.6.7.5.

Table 6.6.7.5 Summary of hierarchical regression analysis for variables predicting levels of adiponectin (n=112).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.236**	**<0.001**	**0.236**	**<0.001**
Age	0.095	0.302				
Sex	**0.488**	**<0.001**				
			0.357	**<0.001**	**0.121**	**<0.001**
Block 2:	0.158	0.74				
Age	**0.475**	**<0.001**				
Sex	**-0.345**	**<0.001**				
BMI	-0.055	0.523				
Psoriatic arthritis			**0.376**	**<0.001**	0.019	0.265
Block 3:	0.166	0.062				
Age	**0.445**	**<0.001**				
Sex	**-0.331**	**0.001**				
BMI	-0.043	0.629				
Psoriatic arthritis	0.078	0.387				
Modified-SPI-i	-0.114	0.197				
PASI			**0.397**	**<0.001**	0.021	0.087
	0.179	**0.044**				
Block 4:	**0.471**	**<0.001**				
Age	**-0.308**	**0.001**				
Sex	-0.024	0.786				
BMI	0.071	0.423				
Psoriatic arthritis	-0.086	0.334				
Modified-SPI-i	0.152	0.087				
PASI						
Total IPAQ scores						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: adiponectin. Statistically significant values are highlighted in bold. Missing data: 4.3%.

Block 1 of the hierarchical regression revealed that age and sex contributed significantly to the regression model ($p<0.001$) and accounted for 23.6% of the variation in adiponectin levels. Introducing BMI and psoriatic arthritis in block 2 explained an additional 12.1% of variance in adiponectin levels. This change in R^2 was found to be significant ($p = <0.001$). Adding the modified SPI-i and PASI variables explained a further 1.9% of variance in levels of adiponectin. However, this R^2 was

not statistically significant. Finally, the addition of physical activity to the regression model explained 2.1% of the variation in levels of adiponectin. However, this change in R^2 was not significant. Together the seven independent variables accounted for 39.7% of the variance in levels of adiponectin. This model, as a whole, was found to be significant ($F = 8.26$, $p = <0.001$). The variables which made a significant contribution to the regression model, in order of importance, include: sex ($\beta = 0.471$, $p<0.001$), BMI ($\beta = -0.308$, $p = 0.001$) and age ($\beta = 0.179$, $p = 0.044$).

6.6.7.6 Physical activity does not explain any of the variance in levels of resistin in people with psoriasis, after controlling from demographic variables and psoriasis severity

A four stage hierarchical multiple regression was conducted with resistin as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI and psoriatic arthritis were entered in block two, the modified SPI-i in block three and total IPAQ scores in block four of the regression. BMI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis). Disease duration and PASI were excluded from the regression as there were no significant correlations observed between these variables and resistin. The results from this multiple regression analysis are presented in table 6.6.7.6.

Table 6.6.7.6 Summary of hierarchical regression analysis for variables predicting resistin levels (n=112).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			0.026	0.298	0.026	0.298
Age	-0.144	0.167				
Sex	0.056	0.586				
			0.036	0.498	0.01	0.617
Block 2:	-0.157	0.145				
Age	0.06	0.563				
Sex	0.103	0.328				
BMI	-0.01	0.927				
Psoriatic arthritis			0.063	0.311	0.027	0.111
Block 3:	-0.182	0.092				
Age	0.057	0.58				
Sex	0.081	0.443				
BMI	-0.052	0.629				
Psoriatic arthritis	0.175	0.111				
Modified-SPI-i			0.063	0.43	0	0.876
Block 4:	-0.181	0.097				
Age	0.059	0.572				
Sex	0.083	0.436				
BMI	-0.05	0.645				
Psoriatic arthritis	0.176	0.112				
Modified-SPI-i	0.017	0.876				
Total IPAQ scores						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: resistin. Missing data: 4.3%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 2.6% of the variation in resistin levels. However, the R^2 change was not significant. Introducing BMI and psoriatic arthritis in block 2 explained an additional 1%, however, this change in R^2 was not significant. Adding the modified SPI-i variable explained a further 2.7% of the variation in resistin levels, however, the change in R^2 was not significant. Finally, the addition of physical activity to the regression model explained 0% of the variation in resistin levels. The R^2 change, upon the addition of physical

activity, was not significant. When all six independent variables were included in the final stage of the regression model it was revealed that none of the variables were significant predictors of resistin levels. Together the six independent variables accounted for 6.3% of the variance in resistin levels. This model, as a whole, was not significant.

6.6.7.7 Sex and BMI were significant predictors of triglyceride levels in people with psoriasis

A four stage hierarchical multiple regression was conducted with triglyceride concentration as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI and psoriatic arthritis were entered in block two, the modified SPI-i in block three and total IPAQ scores in block four of the regression. BMI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis).

For the purpose of this model, participants with diabetes and those on lipid lowering medication were excluded from the analysis.

Disease duration and PASI were excluded from the regression as there were no significant correlations observed between these variables and triglyceride levels. The results from this multiple regression analysis are presented in table 6.6.7.7.

Table 6.6.7.7 Summary of hierarchical regression analysis for variables predicting levels of triglycerides (n=97).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.236**	**<0.001**	**0.236**	**<0.001**
Age	0.129	0.234				
Sex	**-0.263**	**0.017**				
Block 2:			**0.357**	**<0.001**	**0.121**	**<0.001**
Age	0.124	0.252				
Sex	**-0.253**	**0.017**				
BMI	**0.261**	**0.014**				
Psoriatic arthritis	-0.131	0.218				
Block 3:			**0.376**	**<0.001**	0.019	0.265
Age	0.123	0.265				
Sex	**-0.254**	**0.018**				
BMI	**0.259**	**0.016**				
Psoriatic arthritis	-0.134	0.23				
Modified-SPI-i	0.01	0.93				
Block 4:			**0.397**	**<0.001**	0.021	0.087
Age	0.117	0.286				
Sex	**-0.264**	**0.014**				
BMI	**0.245**	**0.024**				
Psoriatic arthritis	-0.154	0.174				
Modified-SPI-i	0.006	0.958				
Total IPAQ scores	-0.109	0.314				

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: triglycerides. Statistically significant values are highlighted in bold. Participants with diabetes and those on lipid lowering medication were excluded from this model (12.8%). Missing data: 4.9%.

Block 1 of the hierarchical regression revealed that age and sex contributed significantly to the regression model ($p<0.001$) and accounted for 23.6% of the variation in triglyceride levels. Introducing BMI and psoriatic arthritis in block 2 explained an additional 12.1% of variance in triglyceride levels. This change in R^2 was found to be significant ($p<0.001$). Adding the modified SPI-i variable explained a further 1.9% of variance in levels of triglycerides, however, this change in R^2 was not

significant. Finally, the addition of physical activity to the regression model explained 2.1% of the variation in levels of triglycerides. This change in R^2 was not significant. Together the six independent variables accounted for 39.7% of the variance in levels of triglycerides. This model, as a whole, was found to be significant ($F = 2.95$, $p<0.001$). The variables which made a significant contribution to the regression model, in order of importance, were sex ($\beta = -0.264$, $p = 0.014$) and BMI ($\beta = 0.245$, $p = 0.024$).

6.6.7.8 Levels of IL-6 in people with psoriasis were not significantly influenced by demographic variables, psoriasis severity or physical activity

A six stage hierarchical multiple regression was conducted with IL-6 as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI was entered in block two, disease duration in block three, psoriatic arthritis in block four, the modified SPI-i in block five and total IPAQ scores in block six of the regression. BMI, disease duration and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis). PASI was excluded from the regression as there was no significant correlation observed between this variables and IL-6 levels. The results from this multiple regression analysis are presented in table 6.6.7.8.

Table 6.6.7.8 Summary of hierarchical regression analysis for variables predicting levels of IL-6 (n=107).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			0.01	0.657	0.01	0.657
Age	-0.015	0.888				
Sex	-0.098	0.361				
			0.034	0.394	0.024	0.145
Block 2:	-0.039	0.72				
Age	-0.092	0.387				
Sex	0.157	0.145				
BMI			0.036	0.533	0.002	0.669
	-0.005	0.971				
Block 3:	-0.082	0.454				
Age	0.148	0.18				
Sex	-0.057	0.669				
BMI			0.038	0.646	0.002	0.646
Disease duration	-0.01	0.939				
	-0.081	0.461				
Block 4:	0.143	0.197				
Age	-0.064	0.632				
Sex	0.051	0.646				
BMI			0.038	0.766	0	0.991
Disease duration	0.01	0.939				
Psoriatic arthritis	-0.081	0.464				
	0.143	0.205				
Block 5:	-0.065	0.635				
Age	0.05	0.659				
Sex	0.001	0.991				
BMI			0.041	0.823	0.003	0.59
Disease duration	-0.001	0.994				
Psoriatic arthritis	-0.072	0.521				
Modified SPI-i	0.151	0.187				
Block 6:	-0.073	0.595				
Age	0.058	0.618				
Sex	0.006	0.959				
BMI	0.061	0.59				
Disease duration						
Psoriatic arthritis						
Modified SPI-i						
Total IPAQ scores						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: IL-6. Missing data: 8.5%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 1% of the variation in IL-6 levels. However, this change in R^2 was not significant. Introducing BMI in block 2 explained an additional 2.4% of variance in IL-6 levels; however, this change in R^2 was also not significant. Adding the disease duration variable explained 0.2% of variance in levels of IL-6, although this change in R^2 was not significant. The addition of psoriatic arthritis also explained 0.2% of variance in IL-6 levels; however, this change in R^2 was not significant. Adding the modified SPI-i variable did not alter the R^2 value (change in R^2 = 0%). Finally, the addition of physical activity to the regression model explained 0.3% of the variation in IL-6 levels. However, this change in R^2 was not significant. Together the seven independent variables accounted for 4.1% of the variance in levels of IL-6. This model, as a whole, was not significant and none of the variables were found to make a significant contribution to the model.

6.6.7.9 BMI was a significant predictor of hs-CRP levels in people with psoriasis

A five stage hierarchical multiple regression was conducted with hs-CRP as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI was entered in block two, psoriatic arthritis in block three, the modified SPI-i in block four and total IPAQ scores in block five of the regression. BMI and total IPAQ scores were entered into the model as continuous variables and modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis). Disease duration and PASI were excluded from the regression as there were no significant correlations observed between these

variables and hs-CRP levels. The results from this multiple regression analysis are presented in table 6.6.7.9.

Table 6.6.7.9 Summary of hierarchical regression analysis for variables predicting levels of hs-CRP (n=104).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			0.006	0.759	0.006	0.759
Age	-0.073	0.507				
Sex	0.027	0.804				
			0.18	**0.001**	**0.173**	**<0.001**
Block 2:	-0.136	0.181				
Age	0.043	0.668				
Sex	**0.421**	**<0.001**				
BMI			**0.18**	**0.002**	0.001	0.778
	-0.13	0.211				
Block 3:	0.043	0.668				
Age	**0.423**	**<0.001**				
Sex	-0.029	0.778				
BMI			**0.188**	**0.004**	0.008	0.372
Psoriatic arthritis	-0.116	0.268				
	0.045	0.656				
Block 4:	**0.435**	**<0.001**				
Age	-0.006	0.957				
Sex	-0.095	0.372				
BMI			**0.206**	**0.004**	0.018	0.182
Psoriatic arthritis	-0.127	0.227				
Modified SPI-i	0.028	0.782				
	0.414	**<0.001**				
Block 5:	-0.021	0.844				
Age	-0.104	0.329				
Sex	-0.139	0.182				
BMI						
Psoriatic arthritis						
Modified SPI-i						
Total IPAQ scores						

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: hs-CRP. Statistically significant values are highlighted in bold. Missing data: 11.1%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 0.6% of the variation hs-CRP levels. However, this change in R^2 was not significant. Introducing BMI in block 2 explained an additional 17.3% of variance in levels of hs-CRP and the change in R^2 was found to be significant ($p = <0.001$). The addition of psoriatic arthritis explained 0.1% of variance in hs-CRP levels; however, this change in R^2 was not significant. Adding the modified SPI-i variable explained a further 0.8% of the variance in levels of hs-CRP, however, this change in R^2 was also not significant. Finally, the addition of physical activity to the regression model explained 1.8% of the variation in hs-CRP levels. However, this change in R^2 was not significant. Together the six independent variables accounted for 20.6% of the variance in levels of hs-CRP. This model, as a whole, was found to be significant ($F = 3.5$, $p = 0.004$). BMI was the only variable found to make a significant contribution to the regression model ($\beta = 0.414$, $p = <0.001$).

6.6.7.10 Physical activity, age, fasting glucose and LDL-cholesterol were all significant predictors of PWV in people with psoriasis

A five stage hierarchical multiple regression was conducted with PWV as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI, psoriatic arthritis, smoking status and alcohol consumption were entered in block two, the modified SPI-I in block three, total IPAQ scores in block four and all of the biomarkers which correlated significantly with PWV in block five. For this model the following biomarkers were included: LDL-cholesterol, sE-selectin, hs-CRP, fasting glucose, triglycerides, insulin, leptin and total-HDL cholesterol ratio. BMI, total IPAQ scores and biomarker concentrations were all entered into the model as continuous variables. Modified SPI-i was entered as a categorical variable (0: no previous

interventions for psoriasis, 1: one or more interventions for psoriasis) along with diabetes (0: no diabetes, 1: presence of diabetes), lipid lowering medication (0: not currently on lipid lowering medication, 1: currently on lipid lowering medication), psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis), smoking (0: not currently a smoker, 1: currently a smoker) and alcohol (0: consumes less than or equal to the recommended amount (i.e. 0-14 units per week for males and females), 1: consumes more than the recommended amount per week). Total cholesterol was excluded from this model on the basis of multi-collinearity. Disease duration and PASI were also excluded from the regression as there were no significant correlations observed between these variables and PWV. The results from this multiple regression analysis are presented in table 6.6.7.10.

Table 6.6.7.10 Summary of hierarchical regression analysis for variables predicting PWV (n=95).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.174**	**0.001**	**0.174**	**0.001**
Age	**0.412**	**<0.001**				
Sex	0.137	0.188				
			0.263	**0.003**	0.089	0.201
Block 2:	**0.345**	**0.002**				
Age	0.155	0.131				
Sex	**0.205**	**0.049**				
BMI	-0.026	0.799				
Diabetes	0.038	0.723				
Lipid lowering medication	0.155	0.145				
Psoriatic arthritis	0.156	0.135				
Smoking	0.005	0.961				
Alcohol			**0.268**	**0.005**	0.004	0.511
	0.337	**0.003**				
Block 3:	0.154	0.136				
Age	0.195	0.063				
Sex	-0.025	0.813				
BMI	0.03	0.778				
Diabetes	0.135	0.219				
Lipid lowering medication	0.155	0.14				
Psoriatic arthritis	-0.001	0.994				
Smoking	0.072	0.511				
Alcohol			**0.271**	**0.008**	0.004	0.557
Modified SPI-i	**0.342**	**0.003**				
Block 4:	0.162	0.122				
Age	0.206	0.055				
Sex	-0.037	0.725				
BMI	0.033	0.763				
Diabetes	0.143	0.2				
Lipid lowering medication	0.151	0.152				
Psoriatic arthritis	0.004	0.968				
Smoking	0.075	0.494				
Alcohol	0.064	0.557				
Modified SPI-i			**0.439**	**0.002**	**0.167**	**0.028**
Total IPAQ scores	**0.253**	**0.023**				
Block 5:	0.256	0.059				
Age	0.011	0.947				
Sex	-0.14	0.192				
BMI	-0.024	0.817				
Diabetes	0.109	0.316				
Lipid lowering medication						
Psoriatic arthritis						

Smoking	0.075	0.47				
Alcohol	0.019	0.859				
Modified SPI-i	0.145	0.177				
Total IPAQ scores	**0.246**	**0.031**				
LDL-cholesterol	**0.42**	**0.036**				
sE-selectin	0.184	0.087				
hs-CRP Fasting	0.078	0.487				
glucose	**0.359**	**0.006**				
Triglycerides	0.209	0.282				
Insulin	0.142	0.264				
Leptin	0.02	0.903				
Total-HDL cholesterol ratio	-0.351	0.202				

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: PWV. Statistically significant values are highlighted in bold. Missing data:18.9%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 17.4% of the variation in PWV and this change in R^2 was significant (p = 0.001). Introducing the BMI, diabetes, lipid lowering medication, psoriatic arthritis, smoking and alcohol variables in block 2 explained an additional 8.9% of variance in PWV. However, this change in R^2 was not significant. The addition of the modified SPI-i variable in block three explained 0.4% of variance in PWV; however, this change in R^2 was not significant. Adding physical activity into the model in block four did not explain any of the variance in PWV (R^2 change = 0.004, p = 0.557). Finally, the addition of the biomarkers (those previously found to correlate with PWV) into the model accounted for 16.7% of the variation in PWV and this change in R^2 was found to be significant. Together the independent variables accounted for 43.9% of the variance in PWV. This model, as a whole, was found to be significant (F = 2.74, p = 0.002). The variables which made a significant contribution to the regression model, in order of importance, included: total IPAQ scores (β = 0.246, p = 0.031), age (β = 0.253 p = 0.023), fasting glucose (β = 0.359, p = 0.006) and LDL-cholesterol (β = 0.42, p = 0.036).

6.6.7.11 Age was a significant predictor of DRA in people with psoriasis

A six stage hierarchical multiple regression was conducted with DRA as the dependent variable. Age and sex were entered into the first block of the regression in order to control for the influence of these demographic variables. BMI, diabetes, lipid lowering medication, psoriatic arthritis, smoking status and alcohol consumption were entered in block two, disease duration in block three, the modified SPI-i in block four, total IPAQ scores in block five and fasting glucose, HbA1C, total cholesterol and total-HDL cholesterol ratio in block six (the biomarkers found to correlate significantly with DRA). BMI, total IPAQ scores and biomarker concentrations were all entered into the model as continuous variables. Modified SPI-i was entered as a categorical variable (0: no previous interventions for psoriasis, 1: one or more interventions for psoriasis) along with diabetes (0: no diabetes, 1: presence of diabetes), lipid lowering medication (0: not currently on lipid lowering medication, 1: currently on lipid lowering medication), psoriatic arthritis (0: no psoriatic arthritis, 1: diagnosed with psoriatic arthritis), smoking (0: not currently a smoker, 1: currently a smoker) and alcohol (0: consumes less than or equal to the recommended amount (i.e. 0-14 units per week for males and females), 1: consumes more than the recommended amount per week). PASI was excluded from the regression as there was no significant correlation observed between this variable and DRA. The results from this multiple regression analysis are presented in table 6.6.7.11.

Table 6.6.7.11 Summary of hierarchical regression for variables predicting DRA (n=100).

Variables	Beta	P value	R^2	Significance of the model	R^2 change	Sig. F change
Block 1:			**0.295**	**<0.001**	**0.295**	**<0.001**
Age	**-0.538**	**<0.001**				
Sex	-0.164	0.083				
Block 2:			**0.332**	**<0.001**	0.037	0.648
Age	**-0.51**	**<0.001**				
Sex	-0.16	0.096				
BMI	0.072	0.452				
Diabetes	0.036	0.707				
Lipid lowering medication	-0.096	0.335				
Psoriatic arthritis	-0.036	0.716				
Smoking	0.035	0.716				
Alcohol	-0.145	0.138				
Block 3:			**0.333**	**<0.001**	0.001	0.763
Age	**-0.508**	**<0.001**				
Sex	-0.157	0.107				
BMI	0.071	0.458				
Diabetes	0.039	0.689				
Lipid lowering medication	-0.098	0.333				
Psoriatic arthritis	-0.037	0.707				
Smoking	0.038	0.699				
Alcohol	-0.147	0.137				
Disease duration	0.029	0.763				
Block 4:			**0.358**	**<0.001**	0.029	0.499
Age	**-0.527**	**<0.001**				
Sex	-0.16	0.097				
BMI	0.05	0.604				
Diabetes	0.043	0.655				
Lipid lowering medication	-0.115	0.251				
Psoriatic arthritis	-0.082	0.417				
Smoking	0.034	0.721				
Alcohol	-0.161	0.101				
Disease duration	0.03	0.756				
Modified SPI-i	0.169	0.097				
Block 5:			**0.374**	**<0.001**	0.016	0.178
Age	**-0.515**	**<0.001**				
Sex	-0.141	0.142				
BMI	0.072	0.457				
Diabetes	0.017	0.86				
Lipid lowering medication	-0.111	0.266				
Psoriatic arthritis	-0.068	0.503				
Smoking	0.029	0.766				
Alcohol	-0.151	0.123				
Disease duration	0.046	0.629				
Modified SPI-i	0.176	0.083				

Total IPAQ scores	0.136	0.178				
Block 6:			**0.403**	**0.001**	0.029	0.751
Age	**-0.514**	**<0.001**				
Sex	-0.147	0.136				
BMI	0.08	0.427				
Diabetes	0.028	0.787				
Lipid lowering medication	-0.103	0.318				
Psoriatic arthritis	-0.064	0.535				
Smoking	0.031	0.748				
Alcohol	-0.152	0.121				
Disease duration	0.047	0.628				
Modified SPI-i	0.173	0.092				
Total IPAQ scores	0.129	0.211				
Fasting glucose	-0.358	0.139				
HbA1C	0.401	0.114				
Total cholesterol	0.096	0.493				
Total-HDL cholesterol ratio	-0.151	0.326				

Beta = Beta-coefficient, R^2 = goodness of fit, R^2 change = variance explained by the variables of interest, Sig. F change = significance of the contribution of independent variables. Dependent variable for this model: DRA. Statistically significant values are highlighted in bold. Missing data: 14.5%.

Block 1 of the hierarchical regression revealed that age and sex accounted for 29.5% of the variation in DRA and this change in R^2 was significant (p = <0.001). Introducing the BMI, diabetes, lipid lowering medication, psoriatic arthritis, smoking and alcohol variables in block 2 explained an additional 3.7% of variance in DRA. However, this change in R^2 was not significant. The addition of the disease duration variable in block three explained a further 0.1% of the variance in DRA. This change in R^2 was not significant. The addition of the modified SPI-i variable in block four explained 2.5% of variance in DRA; however, this change in R^2 was not significant. Adding physical activity into the model in block five explained a further 1.6% of the variance in DRA; however, this change in R^2 was also not significant. Finally, the addition of fasting glucose, HbA1C, total cholesterol and total-HDL cholesterol ratio explained 2.9% of the variation in DRA. This change in R^2 was not significant. Together the independent variables accounted for 40.3% of the variance in DRA. This model, as a whole, was

found to be significant ($F = 3.11$, $p = 0.001$). Age was the only variable which made a significant contribution to the regression model ($\beta = -0.514$, $p<0.001$).

6.6.8 Conclusions from study three

This is the first study to examine the biochemical profile of patients with psoriasis in relation to physical activity, future CVD risk and cardiorespiratory fitness. It was concluded from this study that a key factor influencing the biochemical profile of males and females with psoriasis is the type and quantity of physical activity. This emphasises the need for patients to be given bespoke advice on how to incorporate physical activity into their daily lives.

The current study also observed that the presence of psoriatic arthritis (as well as psoriasis) significantly impacts the biochemical profile of patients. The results from this study may suggest that individuals with comorbid psoriatic arthritis are at higher risk of CVD compared to those with psoriasis only. Therefore, this should be taken into account by the clinician, both when considering treatment options and providing advice on lifestyle interventions.

The results from this study revealed that both sE-selectin and LDL-cholesterol are correlated with disease severity (as measured by PASI) in patients with psoriasis. This may imply that those with severe psoriasis are also at a higher risk of cardiovascular events. However, more work is required to verify this statement, given that participants in this study had relatively low PASI's (median PASI: 4.4).

In this study it was also found that the biochemical profile of patients with psoriasis may be an indicator of arterial stiffness, as measured by PWV. In particular, levels of

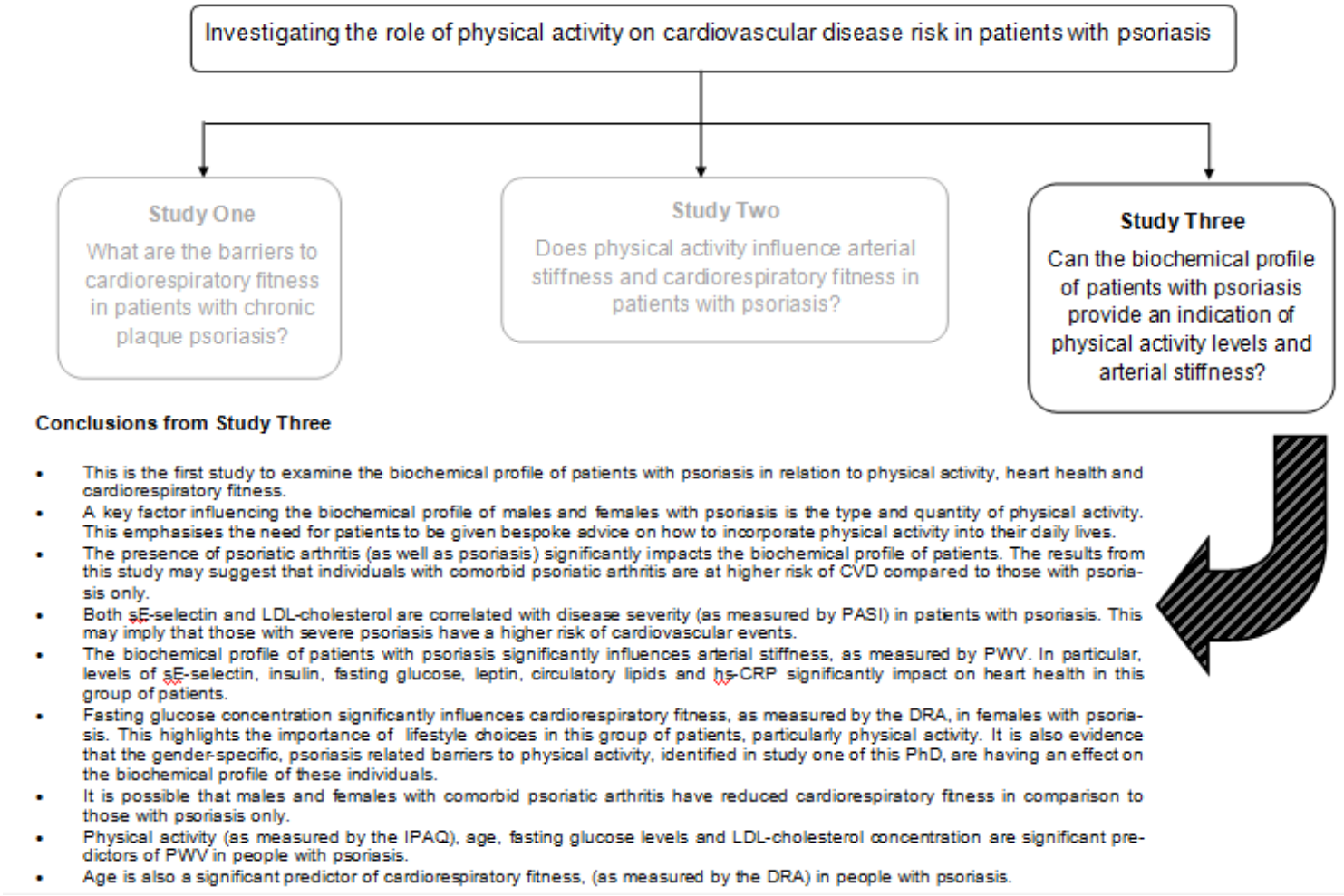
sE-selectin, insulin, fasting glucose, leptin, circulatory lipids and hs-CRP significantly impact on future CVD risk in this group of patients.

Fasting glucose concentration was also found to correlate with cardiorespiratory fitness, as measured by the DRA, in females with psoriasis. This highlights the importance of lifestyle choices in this group of patients, particularly physical activity. It is also evidence that the gender-specific, psoriasis related barriers to physical activity, identified in study one of this PhD, are having an effect on the biochemical profile of these individuals.

The findings from the sensitivity analyses in this study, (whereby individuals with psoriatic arthritis were excluded) indicate a possibility that males and females with comorbid psoriatic arthritis have reduced cardiorespiratory fitness in comparison to those with psoriasis only. This reinforces the notion that advice given to patients should be tailored to their individual needs, depending on factors such as ability and the presence of comorbid conditions.

Finally, it was established that physical activity (as measured by the IPAQ), age, fasting glucose levels and LDL-cholesterol concentration are significant predictors of PWV in people with psoriasis, even after controlling for basic demographics, lifestyle factors, psoriasis severity and factors which may directly impact the concentrations of these biomarkers (including the presence of diabetes and lipid lowering medication). Age is also a significant predictor of cardiorespiratory fitness, (as measured by the DRA), when controlling for such factors in people with psoriasis (see figure 6.6.9 for a summary of the conclusions drawn from study three). These aspects of the current study will be discussed in more detail in chapter seven.

Figure 6.6.8 Summary of the main conclusions drawn from study three of this PhD.



CHAPTER SEVEN: DISCUSSION

7.1 Study One

The overarching research aim of this PhD was to investigate the importance of physical activity on cardiovascular disease risk in patients with psoriasis. In order to address this aim we explored both the behavioural and biological links between psoriasis and cardiovascular disease in the context of physical activity.

Psoriasis-specific barriers to physical activity

Study one of this PhD is the first study highlighting links between low levels of physical activity and poor quality of life in patients with psoriasis. In-depth analysis of the DLQI revealed that the individual items of this questionnaire are key in identifying psoriasis-specific barriers to physical activity. More specifically, it was found that the following psoriasis-specific experiences impacted significantly on levels of physical activity: skin sensitivity (DLQI question [Q] 1), embarrassment (Q2), clothing choice (Q4), social/leisure activities (Q5), engagement in sport (Q6) and treatment (Q10). In particular, skin sensitivity (i.e. how itchy, sore or painful one's skin was) was a distinct barrier to moderate and vigorous-intensity activities for different groups of participants. In this instance psoriasis is acting as a physiological barrier, which is expected given that hot or humid conditions are associated with these types of activities, which can irritate the skin and make people feel uncomfortable and reluctant to engage in such activities. It has been suggested that psoriatic skin is less effective in dissipating heat and may interfere with sweating (Leibowitz et al., 1991). Additionally, it was found that clothing choice was a barrier to moderate and vigorous-intensity activities, particularly in participants over the age of 65. In contrast, Torres et al (2014) also used the IPAQ short-version to compare physical activity in patients

with severe psoriasis and healthy controls. They found that patients with psoriasis

exhibited decreased levels of physical activity in comparison to healthy controls (Torres et al., 2014). The authors speculated that the diminished physical activity of patients with psoriasis may be associated with psychological and physiological barriers. There was no evidence to support this conclusion and no in-depth analysis done to raise such speculation.

These findings suggest that more attention should be paid to patients' responses to individual questions rather than simply looking at the overall DLQI score. The majority of studies in the literature, which have utilised DLQI as an assessment of quality of life in psoriasis, have used the composite DLQI score (Kurwa and Finlay, 1995, Nichol et al., 1996, Torres et al., 2014, Khoury et al., 2014). Therefore, little attention is being paid to the individual items of the DLQI which can mean that the impact of psoriasis on certain aspects of a person's life is overlooked. A low (total) DLQI score does not necessarily indicate that psoriasis is having a low impact on an individual's quality of life.

Other investigators have suggested that the DLQI may not provide an adequate assessment of patients' health-related quality of life in respect of physical activity. However, a validated assessment tool for measuring levels of physical activity in patients with psoriasis was not used;in preference to qualitative information from patient interviews to assess levels of physical activity and the sample size was small (n=8) (Khoury et al., 2014). In contrast, my work found that physical activity was significantly inversely correlated with total DLQI scores ($r = – 0.109$, $p = 0.049$), even before the in-depth analyses of the DLQI. This demonstrates that patients who reported a greater overall impact of psoriasis on their quality of life indicated lower levels of physical activity than those who were less affected by their psoriasis.

Study one, commensurate with previous work, highlights the distinction between physical severity of psoriasis and psychosocial severity (Finlay, 2005, Reich and Griffiths, 2008). Psoriasis is a condition which affects people in different ways and physical severity is often not a reliable indicator of the psychosocial impact of the disease. Previous work has suggested that the impact of psoriasis on quality of life is often underestimated. One study found that that psoriasis has a negative impact on important aspects of patient's lives to an extent comparable to that of other medical conditions including heart disease, diabetes and depression (Reich and Griffiths, 2008). Hence, more recently self-report quality of life measures are now being used in conjunction with the PASI and other objective measures of disease presentation, in order to monitor treatment response (Schafer et al., 2010a). Another study by Rapp et al (1999) assessed health-related quality of life in patients with psoriasis compared to patients with other major chronic health conditions (Rapp et al., 1999). It was found that the impact of psoriasis on health-related quality of life was similar to that of other major medical conditions (such as arthritis, chronic lung disease and cancer) (Rapp et al., 1999). In particular, study one of this PhD supports the use of the DLQI, (a quality of life assessment), to identify psoriasis-specific barriers to physical activity. However, it has also emphasised the importance of individual items of DLQI and how it is key to assess the individual scores for each item as oppose to just taking into account the overall composite score.

Criticisms of the DLQI

The DLQI has been utilised extensively in psoriasis research and test-retest reliability has been shown to be high in numerous studies (Basra et al., 2008, Simpson et al., 2015). However, the DLQI has been criticised for not fully capturing the effect of skin disease on people's emotions and mental health (Badia et al., 1999). The implication of this is that the DLQI may lack conceptual validity, particularly in patients with minor dermatological conditions or in conditions which have a significant impact on mental

health (Both et al., 2007). A further appraisal of the DLQI concluded that the some of the items on the questionnaire did not seem to group logically together (Nijsten et al., 2006). It was also observed that a large proportion of the items on the DLQI provoked very different responses across age and gender (Nijsten et al., 2006, Both et al., 2007). This is particularly important since the DLQI covers various aspects of a person's life. A low DLQI score could lead a clinician to believe that a patient is rather unaffected by their psoriasis when in fact, they have scored highly on one item which means that their psoriasis is having a significant impact on one aspect of their life, which is was was found to be the case in study one. Additionally, specific aspects of life which are affected may depend on age and gender.

Levels of activity in patients with psoriasis

The guidelines provided by the American Heart Association state that moderate and vigorous-intensity physical activity is important in promoting and maintaining cardiorespiratory health (Haskell et al., 2007). Study one of this PhD revealed that vigorous-intensity physical activity is the most problematic type of activity for patients with psoriasis, with respect to psoriasis-specific experiences. Taking this into account, along with the cardiovascular disease risk in this group of patients (Samarasekera et al., 2013), this aspect of patient management should be targeted for intervention.

Other groups have observed that an alarming 18.9% of patients with severe psoriasis (defined as >10% of the body surface area covered by psoriatic lesions) failed to comply with the recommended guidelines for physical activity (n=90). However, in our much larger cohort, it was revealed that 52.8% (45% of males and 60% of females) of patients with psoriasis (median PASI of 2.5) failed to meet the recommended guidelines for physical activity, (independent of psoriasis severity), provided by the AHA.

Consistent with other studies (Armstrong et al., 2012, Armstrong et al., 2013a, Armstrong et al., 2013b, Ma et al., 2013, Torres et al., 2014), study one of this PhD

demonstrated that psoriasis patients whose activity levels are categorised as ‘unhealthy’ (not complying with the recommendations of the AHA) were more likely to have hypertension, be obese and have diabetes (see table 4.6.2 in chapter 4). These are all components of the metabolic syndrome and known risk factors for cardiovascular diseases (Gisondi et al., 2007).

Male and female differences

Multiple linear regressions revealed that sex was the strongest predictor of physical activity, including vigorous-intensity physical activity, in patients with psoriasis. Differences between males and females were consistent in study one of this PhD; we observed a significantly greater proportion of females to males within the study population who did not adhere to the recommended guidelines for physical activity. In the 18-65 age group of patients with psoriasis, it was found that 42% of males and 58% of females took part in less than the recommended amount of physical activity on a weekly basis, whilst in the over 65 age group it was almost 70% of males and almost 74% of females. These findings may suggest that male participants with psoriasis overestimate the duration and intensity of their physical activities, therefore providing more sociably desirable responses. However, previous work has found that self-report physical activity was lower when compared to results of heart rate monitoring, in males (Prince et al., 2008). Also previous studies have observed strong correlation between self-reported physical activity and accelerometer-assessed physical activity in males (Prince et al., 2008, Cust et al., 2008, Hagstromer et al., 2010). An alternative explanation for the greater proportion of females participants failing to meet the guidelines for physical activity could be that the psychosocial burden of psoriasis is more pronounced in women (Sampogna et al., 2006). Studies have shown that women feel significantly higher levels of discrimination (Ginsburg and Link, 1989, Schmid-Ott et al., 2005) as well as disability, stigmatisation, anxiety and depression (Richards et al., 2001). Although, it has been observed that males

report greater work-related stresses which are linked with their psoriasis (Gupta and Gupta, 1995). Other studies have reported no differences in the psychological and social impact of psoriasis between males and females (Gupta and Gupta, 1995).

An additional key finding from study one of this PhD was that psoriasis-specific barriers to physical activity were more prevalent in the female population. The in-depth analyses of the DLQI revealed that feelings of embarrassment or self-consciousness and participation in sporting activities were key barriers to moderate and vigorous-intensity, in particular, in females with psoriasis. A previous study by Leino et al (2014) found that more than half of people with psoriasis (n=262) had either reduced or completely given up at least one of their leisure time activities, of which included exercise and sporting activities (Leino et al., 2014). Additionally, activities which could be expected to cause embarrassment, such as social activities and swimming, were given up by 29% or individuals and reduced by 21.4%. Those who reported a reduction in these types of activities were significantly younger than those who did not reduce these activities (Leino et al., 2014). Females had reduced their time spent on leisure activities by a mean of 129 minutes per week, in comparison to 64 minutes per week in males, although this difference between males and females was not significant (Leino et al., 2014).

Study one of this PhD also found that females aged 18-65 years were a vulnerable group in terms of skin involvement. It was observed that the physical severity of psoriasis, as measured by the PASI, significantly impacted levels of activity engagement in younger females (aged between 18 and 65). This is similar to what was observed in a study by Al-Mazeedi et al (2006), who observed that the severity of a person's psoriasis correlated with level of engagement in physical activity (Al-Mazeedi et al., 2006). However, a validated assessment tool to measure levels of physical activity and they did not examine gender differences. A more recent study found that patients with psoriasis (PASI ≥10) were concerned about how to present

their bodies in sports activities. Participants feared the reactions of others and as a result they avoided fitness centres and public swimming pools. It was also reported that those who did engage in exercise had to think about how to conceal their skin and how to behave in public surroundings (Khoury et al., 2014).

Despite the significant correlation between PASI and physical activity in females aged 18-65 years, the r value was relatively small ($r = -0.187$, $p = 0.046$), indicating a weak relationship between these two variables. It has been suggested that although females with psoriasis are aware of societal stereotypes regarding physical appearance, they are still able to protect themselves from feelings of stigmatisation, (Perrott et al., 2000) which could explain the poor correlation between PASI and physical activity. Alternatively, the weak correlation between these two variables could be explained by a lack of variation in PASI within the study population (PASI range: 0.7-5.5).

Interventions (SPI-i) and physical activity

We describe a significant inverse correlation between intervention scores and vigorous-intensity physical activity scores ($r = -0.398$, $p = 0.05$) in females over the age of 65. However, upon modification of the SPI-i variable, (an indirect measure of psoriasis severity), in order to eliminate disease duration as a confounder and increase the weighting of previous interventions (see section 3.5.2 for more detail), no significant correlations between SPI-i (modified) and physical activity were observed. This suggests that age and/or disease duration may be key factors in influencing levels of activity, particularly in the over 65 female population. Other groups have observed that a prolonged duration of psoriasis significantly increased the likelihood of being forced to give up a leisure- time activity completely (Leino et al., 2014). Another argument for the impact of disease duration on levels of activity is habit formation. It could be that the negative experiences people have had whilst living with psoriasis, particularly during childhood may have resulted in the

formation of habits, such as avoiding physical activity, which have then persisted through to their adult life. A study by Taylor et al (1999) used a sample of 105 healthy males, aged between 32-60 years to look at patterns of physical activity and psychosocial factors during childhood. The results from this study revealed a negative relationship between experiences from childhood and adolescence and current activity levels (Taylor et al., 1999). A similar concept can be applied to psoriasis-specific experiences when it comes to patterns of physical activity. For example, a child with psoriasis may be bullied or stigmatised by their peers due to the visibility of their psoriatic lesions, which can have detrimental psychosocial effects on their quality of life (Lin, 2012). There is a general consensus that habits are acquired through strengthening of an association between a situation or a cue and an action (Lally et al., 2010). So, in the case of a child being bullied during a sports class as a result of their skin, for example, the cue might be the exposure of their psoriatic lesions to their peers and the action would be the comments and behaviour from those individuals. Consequently, the child may become reluctant to attend the class. In terms of physical activity, these types of experiences may make people reluctant or unwilling to engage in certain types of activities or even any activity at all – a form of avoidance coping, whereby individuals avoid situations where they feel they will be stigmatised on the basis of their skin (Fortune et al., 1997b).

An alternative explanation for the poor correlations observed between the SPI-i component and physical activity could perhaps be due to low PASI (median PASI: 2.5), which indicate clear or mildly affected skin. Participants with high SPI-i scores are likely to have undergone various treatments for their psoriasis, some of which may have been very effective. Therefore, the physical burden of psoriasis may not be significant for these participants when it comes to them engaging in physical activities. Conversely, high SPI-i scores could indicate very stubborn, problematic psoriasis

which, consequently, could act as a significant burden to individuals when engaging in physical activity. However, lack of variation (narrow IQR for PASI:1.9-8) in our study population may restrict such discrimination.

Evaluating the International Physical Activity Questionnaire

The primary tools used in this study were the IPAQ and DLQI. A disadvantage of using these instruments is that they provide only a 'snap-shot' of the previous seven days, preventing us from monitoring how the impact of a person's psoriasis on their quality of life may affect their engagement in physical activity over a prolonged period of time. However, the benefit of using them concurrently was that we were able to obtain a reliable view of how one may have affected the other during the seven days in question.

The IPAQ short-version was used in order to reduce the burden on participants. The IPAQ is a well-developed set of instruments, which has been validated in different languages and can be used to obtain comparable estimates of physical activity over the last seven days (Craig et al., 2003). One disadvantage of using the short-version IPAQ is that it does not account for occupational activity whereas the long-version collects detailed information regarding job-related physical activity. However, tests of reliability and validity found that the exclusion of occupational activity did not significantly influence correlations between long and short forms of the questionnaire.(Craig et al., 2003). This shows that the short-version IPAQ provides a global estimate of total physical activity including a comparable amount of job-related activity (Craig et al., 2003).

The IPAQ was designed to be used by adults aged 18-65 however, the age range of patients within this cohort is 19-90. Although this is unlikely to have had a significant impact on the results of this study, as the recommendations for maintenance of

cardiorespiratory fitness are very similar for those aged between 18 and 65 and those aged over the age of 65 (Nelson et al., 2007).

Additionally, the IPAQ has been shown to overestimate physical activity, when compared with data measured by an accelerometer, which is an objective method of measuring physical activity (Lee et al., 2011, Dyrstad et al., 2014). Therefore, the levels of physical activity of the participants in this study may have in fact been even lower than what was reported in our study. Generally, self-report of physical activity is often interpreted with caution as participants frequently overstate the time and intensity of their activities. One of the main reasons for overstating physical activity may be to present oneself in a positive light by providing sociably desirable responses (Rzewnicki et al., 2003).

The IPAQ is a particularly useful tool for identifying the type of physical activity which people are participating in as it asks individuals to record the length of time they spent walking (mild activity) as well as how long they spent engaging in moderate and vigorous-intensity activity.

Strengths of study one of this PhD

This is the first study to highlight a relationship between low levels of physical activity and quality of life in patients with psoriasis. The findings from this study support the argument for psoriasis as a contributing factor to CVD as oppose to an independent risk factor. A lack of physical activity, or perhaps certain type of activities (i.e. moderate/vigorous-intensity activities), may contribute to the development of the metabolic syndrome, which in turn can promote the risk of CVD. In this instance it was observed that some psoriasis-specific experiences were negatively impacting on levels of physical activity.

A strength of this study was that it emphasised the importance of the DLQI and how it can be used to identify psoriasis-specific barriers to physical activity, which is

important given the high prevalence of the metabolic syndrome and CVD risk in this group of patients. This suggests that perhaps this area of patient management should be targeted for intervention. Another strength of this study is that the study cohort consisted of patients with mild-moderate psoriasis. The median PASI in this group of patients was 2.5 which is unlike previous studies which tend to recruit patients with moderate-severe psoriasis (usually defined as having a PASI >10). Finally, another strength of this study was that validated assessments of psoriasis severity (including DLQI, PASI and SPI) and physical activity (i.e. the IPAQ) were used, which is unlike some previous work in this field.

Limitations of study one of this PhD

A limitation of this study is the lack of a healthy control cohort. For future work it would be valuable to have a control group in order to compare levels of physical activity between patients with psoriasis and healthy volunteers. Another limitation of this study is the use of self-report measures to assess physical activity. People often provide sociably desirable responses which may not reflect the 'true' level of physical activity in which they engage in (Rzewnicki et al., 2003). For future work it would be useful to use an objective measure of physical activity in order to assess the accuracy of people's responses to the IPAQ. Future work will be discussed later in this chapter.

7.2 Study Two

This is the first study to investigate the relationships between PWV, DRA and self-report patterns of activity, in a psoriasis population. The results from this study show that future CVD risk, as measured by PWV is closely correlated (inverse relationship) with cardiorespiratory fitness, as measured by the DRA. Studies which are present in the literature are usually in populations of patients with coronary artery disease

(Ikonomidis et al., 2015a, Tritakis et al., 2016), which has allowed for the documentation of the principles of pulse wave analysis and wave reflections. Typically, in a healthy arterial system when PWV is low, the backward reflected wave arrives at the ascending aorta late during diastole (when the heart muscles realx and the ventricles fill with blood), therefore increasing coronary perfusion (Ikonomidis et al., 2015a). In contract, increased arterial stiffness causes the reflected waves to arrive in early systole (contraction of the heart muscles). Consequently, the pressure in the wall of the left ventricle during ejection is increasesd, thus leading to an elevated oxygen demand and a reduction in coronary perfusion. Over time, elastic properties of the arteries become abnormal which results in arterial stiffness, either in the presence or absence of heart disease (Ikonomidis et al., 2015a). DRA is derived by the duration of diastole and the area between the theoretical diastolic pressure curve without reflection and the actual (measured) diastolic pressure curve with reflection. The DRA provides an indication of the quality of diastolic filling, therefore, the higher the DRA the better the filling condition of the left coronary artery during diastole (Tritakis et al., 2016). Taking this into account, it was expected for the PWV and DRA parameters to be significantly inversely correlated in patients with psoriasis.

Study two revealed that the type of physical activity is a key factor in determining PWV. It was found that PWV and vigorous-intensity physical activity scores were significantly, inversely correlated, particularly in males with psoriasis, aged 18-65**.** These results imply that the quantity of energy expended during exercise is key for arterial stiffness and future CVD risk. Further examination of PWV amongst the 3 levels of activity (categorical IPAQ score) highlighted significant differences in PWV between categories 2 (moderate level of activity) and 3 (high level of activity), therefore emphasising the importance of the type and quantity of activity, particularly in individuals aged 18-65. Previous work has emphasised the importance of high-intensity physical activity in preventing cardiovascular diseases (Rognmo et al., 2012,

Francois and Little, 2015). Other groups have shown that individuals who followed a HIIT programme for 12-16 weeks (three times per week) had significantly enhanced vascular-dependent function in comparison to individuals who followed a MICT programme (Wisløff et al., 2007, Tjønna et al., 2008). It has been postulated that the ability of HIIT to improve vascular function may be due to the increased blood flow through the vessels supplying oxygen to the working muscles, which subsequently promotes greater shear stress-induced nitrous oxide bioavailability (Wisløff et al., 2007, Tjønna et al., 2008, Ramos et al., 2015). This is supported by previous work by Thijssen et al (2009) who found that blood flow and shear stress increased with increasing intensity of activity (Thijssen et al., 2009).

Additionally, previous work has shown that patients with psoriasis have significantly higher PWV values than healthy controls, but also they have similar PWV values to patients with coronary artery disease, even after adjustment for atherosclerotic risk factors (Ikonomidis et al., 2015b). Taking into account the relationship between vigorous-intensity activity and PWV, along with the cardiovascular disease risk in this group of patients, this aspect of patient management could be targeted for intervention. Furthermore, PWV could be a means to monitor future CVD risk in a non-invasive, efficient way.

Study two also found that cardiorespiratory fitness, (as measured by DRA) is significantly correlated with self-report levels of moderate and vigorous-intensity physical activity, particularly in males and females with psoriasis, aged 18-65. It is evident that the type of activity is a key factor in determining cardiorespiratory fitness in patients with psoriasis. DRA values also varied significantly between the low-levels (category 2) of activity and the high-levels of activity (category 3) groups in participants with psoriasis, aged 18-65 years. Previous work has shown improvements in cardiorespiratory fitness as measured by either maximal oxygen uptake or peak oxygen uptake, following 12 weeks of HIIT, three times per week

compared with MICT. A study by Mitranun et al (2014), with Type 2 diabetic adults, found that individuals on the HIIT programme had greater improvements in their aerobic fitness as well as improvements in lipid profiles and glycemic control (Mitranun et al., 2014). My work also found that DRA values were significantly lower in people with psoriasis, aged 18-65, who failed to meet the AHA guidelines for physical activity. Additionally, the DRA was sensitive to sedentary behaviour, particularly in females with psoriasis, aged 18-65. These results suggest that the DRA is potentially a surrogate measure for the amount of heart-healthy exercise undertaken in the immediate several days/weeks. Although further calibration is required, DRA could be a means to 'measure' exercise and be a more objective way of doing so than a self-report tool.

Finally, the results from study three revealed that age, smoking and treatment for hypertension are significant predictors of arterial stiffness, as measured by PWV in patients with psoriasis. These factors are key CVD risks and are often present in healthy controls. These findings present specific factors to target in the psoriasis population.

It is well-established that smoking can increase a person's risk of various diseases, however, in a psoriasis population, smoking may also contribute to the exacerbation of psoriatic lesions. One study found that the intensity (number of cigarettes smoked each day) of a patient's smoking was related to the severity of psoriasis, even after controlling for various confounding factors, including age, sex, stress and alcohol consumption (Fortes et al., 2005). Patients who smoked more than 20 cigarettes each day were likely to have a more severe case of psoriasis than those patients who smoked less than or equal to 10 cigarettes per day (Fortes et al., 2005). Therefore, it is in the interest of these patients to either reduce their number of cigarettes or stop smoking completely and, given the potential increased risk of CVD in this population

and that smoking is a modifiable lifestyle factor, it should be targeted for intervention. Similarly, for individuals being treated for hypertension the focus for intervention could be on both how to improve pre-existing hypertension and on preventative methods, such as advice on health-promoting lifestyle choices.

Study three revealed that age was a significant predictor of both arterial stiffness (PWV) and cardiorespiratory fitness (DRA). Unlike other modifiable lifestyle factors, such as smoking and exercise, age is not modifiable. Therefore, in order to target the age-related decline in heart health and cardiorespiratory fitness in this group of patients, the focus could be on medical education, with emphasis on risk communication and ways to help maintain a heart-healthy lifestyle (Keyworth et al., 2015). This is likely to be increasingly important as the population, as a whole, ages and whilst psoriasis has no cure (and remains a life long disease in those it aflicts).

Strengths of study two

A key strength of this study is that it is the first study to assess DRA in relation to physical activity and arterial stiffness in patients with psoriasis. Additonally, PWV and DRA were identified as potential objective, non-invasive 'measures' of future CVD risk and levels of physical activity/cardiorespiratory fitness, respectively, in patients with psoriasis.

Limitations of study two

A limitation of this study is that the data set relies on information from a self-report tool – IPAQ. It is possible that this introduces some reporting bias and a more objective measure of exercise engage,ment would be helpful. In addition the investigations into the novel parameter DRA is hampered due to a lack of lack other studies / data in the literature and normal ranges / reference points.

7.3 Study Three

Study three of this PhD is the first study to examine the biochemical profile of patients with psoriasis in relation to physical activity, arterial stiffness and cardiorespiratory fitness. One of the key observations from this study was that the type and quantity of physical activity was a principal influencing factor on the biochemical profile of patients with psoriasis. Additionally, in males with psoriasis significant relationships were observed between biomarker concentrations and vigorous-intensity activity. More specifically, in males, vigorous-intensity activity was significantly inversely correlated with levels of sE=selectin, insulin, leptin and triglycerides. In contrast, in females biomarker concentrations tended to be significantly correlated with mild-intensity activity (walking) and total IPAQ scores (the sum of mild, moderate and vigorous-intensity activities). More specifically, in females both mild-intensity (walking) activity and total activity (i.e. total score for mild, moderate and vigorous-intensity activities) were significantly inversely correlated with levels of insulin, fasting glucose, leptin, triglycerides and hs-CRP. Total activity also correlated with levels of adiponectin and total-HDL cholesterol ratio in females. This indicates a contrast in the type or intensity of physical activities in which males and females with psoriasis choose to engage in. Taking this into account, along with the results presented in study one (chapter four) of this PhD, it is evident that psoriasis-specific barriers to physical activity, particularly vigorous-intensity activity, are more prevalent in females. Also females seem to be opting for lower-intetnsity activities, however, significant correlations between their activity levels and specific parameters within their biochemical profile were observed in study three (chapter six). A recent study by Ghafourian et al (2016) reported that exercise of a lower-intensity is more effective than high-intensity exercise in reducing inflammation (Ghafourian et al., 2016).

The effects of physical activity on the biochemical profile of any individual can vary depending on whether they engage in activity on a short or long-term basis. It has been established that isolated bouts of physical activity can produce acute, transient cardiovascular and metabolic responses. Regular physical activity on the other hand, elicits more permanent responses (Thompson et al., 2001, Ploeger et al., 2009). An example of this comes from circulatory lipids; physical activity has been shown to acutely reduce levels of triglycerides and LDL-cholesterol and increase levels of HDL-cholesterol (Bounds et al., 2000, Grandjean et al., 2000) However, these metabolic changes are transient and may only persist for up to 72 hours (Thompson et al., 2001). The extent of these effects can also depend on energy expenditure (i.e low, moderate or high levels of activity). Generally, these effects appear to increase with energy expenditure (Ploeger et al., 2009). Previous work has also shown that metabolic markers, such as glucose, can be reduced and insulin sensitivity can be enhanced following a single bout of moderate exercise in participants who are insulin-resisant (Perseghin et al., 1996). However, a reduction in glucose levels has also been observed in healthy participants following a short-term period (10 days) of submaximal exercise (Mendenhall et al., 1994). These effects on metabolic markers are likely to be maintained by regular exercise and it has been shown that these effects correlate with exercise intensity (i.e. the greater the intensity, the greater the reduction of these markers will be) (Thompson et al., 2001). Alteration in levels of adipokines in response to physical activity have also been observed. However, the effects of exercise on levels of adipokines can vary between short (<12 weeks) and long-term (>12 weeks) training. Transient reductions in leptin levels and elevation in adiponectin levels are seen during short-term periods of activity. However, in order to sustain these effects, long-term, consistent exercise is required (Bouassida et al., 2008). It has also been observed that levels of inflammatory markers, including hs-CRP and TNF-α can increase following a bout of exercise. However, studies have shown that longitudinal exercise training or regular bouts of physical activity can

produce a long-term anti-inflammatory effect (Kasapis and Thompson, 2005). Similarly, levels of sE-selectin are markably reduced with regular bouts of physical activity over a longer period of time, for example 8-12 weeks (Saetre et al., 2011, Jalaly et al., 2015).

In light of this it is important to take into account the altered biochemical profile of individuals with psoriasis. Previous research has shown that people with psoriasis have higher levels of cell adhesion molecules and markers of inflammation, including sE-selectin and hs-CRP in comparison to healthy controls (Martinez-Sales et al., 2015). It has also been observed that levels of triglycerides, LDL-cholesterol and total cholesterol are elevated in psoriasis patients in comparison to non-psoriatic individuals, whilst levels of HDL-cholesterol are lowered (Akkara Veetil et al., 2012). Other studies have also reported altered adipokine profiles in patients with psoriasis; levels of leptin and resistin are enhanced in these individuals and levels of adiponectin are redcued (Coimbra et al., 2010). This dysregulation of the biochemical profile of patients with psoriasis can contribute to the development of the metabolic syndrome and predispose individuals to CVD. Hence, there is currently a big emphasis on the importance of modifiable lifestyle choices, particularly physical exercise. Little work has been done regarding the optimal threshold required to yield beneficial effects on a person's biochemical profile. Even less work has been done in a psoriasis population. Hence, the results of my study are pivotal as they emphasise that patients with psoriasis can alter, through exercise, their biochemical profile, in spite of the constituative inflammatory drive from their psoriasis. My results also highlight the importance of the type, intensity and duration of physical activity on a range of biomarkers in patients with psoriasis. Although there is still work to be done, these results mark a platform for future work (see future work section for more detail). The message from my study is that the magnitude of changes on biochemical profile elicited through engagement in physical activity in patients with a psoriasis, a chronic

inflammatory condition, is important to monitor in order to ensure that inflammation is not being amplified and that people are exercising in both a heart-healthy way and in a way that is appropriate for their health status (Ploeger et al., 2009).

When looking at the effects of physical activity on biochemical profile there are a variety of confounding factors to take into consideration. Such factors may include: age, gender, BMI, presence of comordities (for example psoriatic arthritis) and even treatments for psoriasis. The results presented in chapter six (study three) highlight the importanct of these factors. BMI in particular, was a significant predictor of insulin, fasting glucose, leptin, leptin, adiponectin, triglycerides and hs-CRP levels in patients with psoriasis. There is currently a large emphasis on the link between obesity and psoriasis, both of which are inflammatory conditions (Coimbra et al., 2009). However, there is controversy surrounding this link in that some believe that obesity is a consequence of psoriasis and some believe the presence of obesity exacerbates the symptoms of psoriasis. Alternatively, it is thought that the two conditons coexist due to the mutual inflammatory component (Coimbra et al., 2016).

Previous work has suggested that obesity as a result of psoriasis could be due to a sedentary lifestyle or avoidance of physical exercise (Herron et al., 2005). The results presented in chapter four (study one) of this thesis could provide an argument for this theory, given that it was identified that patients with psoriasis face psoriasis-specific barriers to physical activity which results in an overall reduction in their activity levels. It has also been proposed that obesity may contribute to the worsening of psoriatic lesions by providing a chronic level of low-grade inflammation (Coimbra et al., 2016, Tobin et al., 2014). In obese individuals the function of adipose tissue and the adipokine profile are altered. The imbalance in the production of pro- and anti-inflammatory adipokines and the hypoxic mileu contribute to the chronic, low-grade inflammatory environment in the body (Suganami and Ogawa, 2010). Thererfore

when psoriasis and obesity coexist, chronic inflammation, a characteristic of both coniditons, is enhanced (Coimbra et al., 2016).

It has been established that physical activity has an anti-inflammatory effect, independent of BMI (Petersen and Pedersen, 2005, Frankel et al., 2012). Previous work has found that physical activity can reduce the levels of pro-inflammatory markers such as TNF-α and IL-6, and increase the levls of anit-inflammatory markers such as adiponectin (Frankel et al., 2012). The data presented in chapter six (study three) of this thesis supports the hypothesis that physical activity can have an anti-inflammatory effect, in a psoriasis population.

Limitations of the use of the International Physical Activity Questionnaire in study three

Taking into account the cross-sectional nature of study three of this PhD, it is difficult to generalise participants' patterns of physical activity (calculated from the IPAQ) to the rest of their lives. The IPAQ provides only a snap shot of the type and quanitity of activity individuals have engaged in over the previous 7 days. This means that activity scores may not be representative of a person's 'normal' activity patterns. For example, an individual who is highly active may have completed the IPAQ at the time of an injury or a unusually busy work schedule whereby they were unable to participate in any physical activity, in which case their activity levels may have been low. Additionally, the overestimation of physical activity is a known issue with the IPAQ and therefore activity levels measured using this questionnaire should be interpreted with caution (Wanner et al., 2016). Previous research has also shown that adherence to regular physical activity in the general population is poor (Allen and Morey, 2010). Although, studies have reported correlations between IPAQ and accelerometer data, assumptions cannot be made (Hagstromer et al., 2010).

Consequently, this makes it more difficult to determine the long-term clinical implications of physical activity on the biochemical profile of patients with psoriasis as causality cannot be assumed. For these reasons, the PWV and DRA parameters were assessed in order to provide a more complete overview of cardiorespiratory health and fitness in relation to biochemical profile in patients with psoriasis. These results will be discussed later in this section.

PASI and the biochemical profile of patients with psoriasis

The results from study three (presented in chapter six) revealed that levels of sE-selectin correlated with disease severity, as measured by the PASI in patients with psoriasis. Adiponectin was also found to be significantly inversely correlated with PASI. Additionally, levels of LDL-cholesterol were found to correlate with PASI specifically in females with psoriasis.

There is controversy in the literature surrounding the relationship between levels of sE-selectin and psoriasis severity (Dowlatshahi et al., 2013). In previous studies that have reported significant correlations between disease severity and levels of sE-selectin, the study populations usually consist of participants with severe psoriasis (Szepietowski et al., 1999, Groves et al., 1995). Similarly, CVD risk has been reported to be higher in individuals with severe psoriasis (Mallbris et al., 2004, Horreau et al., 2013). Given that sE-selectin has been established as a marker for CVD in psoriasis (Laws et al., unpublished, Hwang et al., 1997), the results from my study could imply that even people with mild psoriasis are at risk of developing CVD.

There is also controversry surrounding the relationship of adiponectin levels with PASI, some studies report no significant relationship between these two variables (Kaur et al., 2011, Gerdes et al., 2012, Madanagobalane et al., 2014). In contrast others have reported a significant positive correlation between adiponectin and

disease severity (Sereflican et al., 2016). However, in my study, a significant inverse correlation was observed between PASI and adiponectin. These findings were similar to those reported by other groups and suggestive that adiponectin may exert a potentially cardio-protective role in patients with psoriasis (Boehncke et al., 2011a).

Concurrent with existing lliterature (Antonucci et al., 2014), the results from my study revealed that LDL-cholesterol was significantly correlated with PASI in females with psoriasis. In males with psoriasis, there was no significant relationship bwtween these two variables. Generally, females have a higher body fat percentage than men due to gender differences in lipid metabolism (Blaak, 2001). Given that previous work has found that oxidised LDL's accumulate in psoriatic skin (Tekin et al., 2007), it could be that the higher percentkage of adipose tissue in females is contributing to the exacerbation of psoriasis symptoms. In turn this may also mean that females with psoriasis are at a higher risk of developing atherosclerotic disease in comparison to males with psoriasis.

Arterial stiffness and biochemical profile in patients with psoriasis

The results from study three (presented in chapter six) showed that the biochemical profile of patients with psoriasis significantly influenced arterial stiffness, as measured by PWV. Assessment of the study group as a whole highlighted a significant correlation between levels of sE-selectin and arterial stiffness. sE-selectin has been independently associated with the metabolic syndrome (Ingelsson et al., 2008, Peng et al., 2013) and has been established as a marker for endothelial dysfunction which is a pre-clinical indicator of atherosclerotic disease (Thorand et al., 2006). In a psoriasis population it has been observed that individuals have increased levels of sE-selectin in comparison to non-psoriatic controls (Long et al., 2010). Taken together

with the results from my study, it is likely that patients with psoriasis are at an increased risk of developing CVD.

Study three also revealed that in males, arterial stiffness was significantly correlated with levels of insulin, leptin, total cholesterol, total-HDL cholesterol ratio, triglycerides and hs-CRP, and significantly inversely correlated with HDL-cholesterol. In females, arterial stiffness was significantly correlated with levels of fasting glucose, total cholesterol, LDL-cholesterol and total-HDL cholesterol ratio. Consistent with previous studies, these findings reinforce the link between a pro-inflammatory environment and arterial stiffness and the development of atherosclerotic disease (Frostegard et al., 1999, Libby, 2006, Frostegård, 2013), particularly in a psoriasis population.

Upon regression of the data, factors which were found to be significant predictors of PWV, even after controlling for various confounding factors, were: physical activity (as measured by the IPAQ), age, fasting glucose levels and levels of LDL-cholesterol. These findings suggest that levels of both fasting glucose and LDL-cholesterol may be independent predictors of aterial stiffness, as measured by PWV, in people with psoriasis. Similar findings have previously been observed in a population of young individuals with psoriasis (Yiu et al., 2011).

Cardiorespiratory fitness and biochemical profile in patients with psoriasis

The results from study three (presented in chapter six) showed that cardiorespiratory fitness, as measured by DRA significantly influenced the biochemical profile of patients with psoriasis. Very little work has been done previously investigating the relationship between biochemical profile and cardiorespiratory fitness in a psoriasis population. Additionally, there are no studies in the current literature using DRA as a measure of cardiorespiratory fitness, in people with psoriasis.

A previous study with revascularised coronary artery disease patients found that DRA was significantly, inversely correlated with vascular inflammation, as measured by lipoprotein phospholipase A2. This biomarker is associated with the development of atherosclerosis and CVD (Carlquist et al., 2007). Generally, the higher the DRA, the better the coronary perfusion is. Similarly, in the current study (study three) a significant inverse correlation between levels of cholesterol and cardiorespiratory fitness was observed. Additionally, in females with psoriasis, DRA was found to be significantly, inversely correlated with levels of fasting glucose. Taken together with the findings on physical activity, PWV and biochemical profile in these patients, these results indicate that lipid and glycaemic control is important for the future CVD risk of patients with psoriasis (particularly females), and that regulation of these biochemical parameters can be enhanced by physical activity.

Upon regression of the data in study three, age was found to be the only significant predictor of DRA in people with psoriasis. Previous research has shown that cardiorespiratory fitness declines with age in the general population. A decrease in VO2 max (defined as the maximum rate of oxygen consumptopm during exercise) of approximately 1.6% per year, has been reported in both men and women (Hakola et al., 2011). It has been established that in individuals who do not take part in regular activity, there is a higher rate of decline in VO2 max with age (Fleg et al., 2005). Low cardiorespiratory fitness is a key risk factor for the development of CVD, as well as obesity and premature mortality, which can also increase which advancing age (Hakola et al., 2011, Baur et al., 2012). Upon reflection of the results presented in chapter four (study one), it is evident that there are age-specific, psoriasis-related barriers to physical activity which in turn may contribute to the decline in cardiorespiratory fitness in this group of patients. In particular, people who do not habitually engage in physical activity may avoid activities which they perceive to require a large amount of effort (Fleg et al., 2005). In study one, the older population

of patients with psoriasis indicated clothing choice as a barrier to physical activity. Consequently, these lifestyle choices in these patients could lead to an accelerated decline in aerobic capacity which in turn may cause further avoidance of physical activity (Fleg et al., 2005).

Once again, given the CVD risk in patients with psoriasis, these findings strengthen the need for tailored advice for patients on lifestyle choices. More specifically, in the interest of maintaining heart health and cardiorespiratory fitness, advice should be given on how to incorporate physical activity into their daily routine and what type of activity would be most appropriate for them as individuals, whilst giving careful consideration to their age and ability.

Impact of psoriatic arthritis on physical activity, arterial stiffness and cardiorespiratory fitness

The results from study three (presented in chapter six) indicate that the presence of psoriatic arthritis significantly impacts on the biochemical profile of patients with psoriasis. Previous work has found that different types of inflammatory arthritis, including psoriatic arthritis, can contribute to a prothrombotic predisposition, including an increase in pro-inflammatory cytokines and a locally activiated endothelium, in patients (Beinsberger et al., 2014). This may indicate that patients with psoriasis are at a greater risk of CVD in comparison to those with psoriasis only (Parisi et al., 2015). A recent study by Parisi et al (2015) poposed that patients with psoriasis have an increased prevalence of comorbidities associated with CVD (Parisi et al., 2015). This study also reported that the risk of a major cardiovascular event was 36% higher in patients with psoriasis who had inflammatory arthritis compared with those who did not (Parisi et al., 2015). However, in some patients the risk may be reduced as a result of psoriasis treatment. For example, methotrexate or inhibitors of TNF-α can

help to normalise pro-inflammatory factors (Beinsberger et al., 2014). We also found that males and females with comorbid psoriatic arthritis may have reduced cardiorespiratory fitness in comparison to those with psoriasis only. In people with psoriatic arthritis there are obvious barriers to physical activity, for example, joint pain (Balato et al., 2014), however, we need to conduct further work to determine other potential barriers in these patients.

Strengths of study three

A key strength of this study is that it is the first study to assess biochemical profile in relation to arterial stiffness (PWV) and cardiorespiratory fitness, as measured by DRA, in a psoriasis population. Additionally, this study covered a vast range of biomarkers in order to thoroughly investigate these relationships.

The findings from study three support the potential risk of CVD in patients with psoriasis, however, they also provide an argument against the risk of CVD in patients with only severe psoriasis (Benson and Frishman, 2015). The median PASI in all three studies was less than 5, indicating psoriasis of relatively mild severity. This may indicate that CVD risk in patients with psoriasis is independent of disease severity, as measured by PASI.

Limitations of study three

A limitation of this study is the relatively small sample size of 117 participants; replication in a larger cohort would be useful.

Standardised measurement of distance between suprasternal notch (jugulum) to the pubic symphysis, in order to calculate PWV, is crucial as even small variations in the distance measurements can generate different PWV values (Van Bortel et al., 2012).

In this study the same device and technique was used for all participants in an attempt to standardise this measure. In addition, all measurements were taken by the same investigator and validation/calibration studies were carried out to ensure reproducibility.

Summary Statement

The debate in the literature as to whether psoriasis is an independent risk factor for CVD or simply a contributing factor is still ongoing (Benson and Frishman, 2015). However, taking into account the findings from previous studies, supporting both of these arguments, along with the results from my three studies, it seems plausible that CVD risk in psoriasis is due to an interaction of psoriasis pathogenesis and behaviour and lifestyle choices of those who suffer with the disease.

This reinforces the importance of lifestyle factors in this group of patients and how clinicians need to think more carefully about the advice they give to patients on how to modify their lifestyles in a heart-healthy way. Special consideration should be given to age, physical ability and the presence of comorbid conditions such as psoriatic arthritis.

7.4 Future work

Moving forward from the work presented in this thesis a future study comparing objective measurement of exercise with patient-reported activity would provide a means to investigate beliefs and attitudes to exercise in the psoriasis population. Each participant could wear an Actiheart device which combines measurement of movement / energy output with heart rate monitoring to provide an objective measure

of activity and heart health. The development of novel technologies and applications may facilitate research in this area, particularly in terms of patient attitudes to exercise and how these may be modified.

Clearly, designing a bespoke exercise programme for patients with psoriasis, addressing the key barriers to exercise in this group, could provide significant health benefits.

Additionally, it would be valuable to examine, in a prospective cohort, the benefits of regular exercise in psoriasis management, assessing factors such as skin control, quality of life and impact on comorbidity.

REFERENCES

ARMSTRONG, A. W., HARSKAMP, C. T. & ARMSTRONG, E. J. 2013b. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. *JAMA Dermatol,* 149, 84-91.

ARONSON, D., SHEIKH-AHMAD, M., AVIZOHAR, O., KERNER, A., SELLA, R., BARTHA, P., MARKIEWICZ, W., LEVY, Y. & BROOK, G. J. 2004. C-Reactive protein is inversely related to physical fitness in middle-aged subjects. *Atherosclerosis,* 176, 173-179.

ASHCROFT, LI WAN, P., WILLIAMS & GRIFFITHS 1999. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *British Journal of Dermatology,* 141, 185-191.

ASHOR, A. W., LARA, J., SIERVO, M., CELIS-MORALES, C. & MATHERS, J. C. 2014. Effects of Exercise Modalities on Arterial Stiffness and Wave Reflection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS One,* 9, e110034.

ASMAR, R., BENETOS, A., TOPOUCHIAN, J., LAURENT, P., PANNIER, B., BRISAC, A. M., TARGET, R. & LEVY, B. I. 1995. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension,* 26, 485-90.

AZEVEDO, M., ARAÚJO, C., REICHERT, F., SIQUEIRA, F., DA SILVA, M. & HALLAL, P. 2007. Gender differences in leisure-time physical activity. *International Journal of Public Health,* 52, 8-15.

AZFAR, R. S. & GELFAND, J. M. 2008. Psoriasis and metabolic disease: epidemiology and pathophysiology. *Current opinion in rheumatology,* 20, 416-422.

BADIA, MASCARÓ, LOZANO & ON BEHALF OF THE CAVIDE RESEARCH, G. 1999. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. *British Journal of Dermatology,* 141, 698-702.

BALASUBRAMANIAM, P., STEVENSON, O. & BERTH-JONES, J. 2004. Fumaric acid esters in severe psoriasis, including experience of use in combination with other systemic modalities. *British Journal of Dermatology,* 150, 741-746.

BALATO, N., MEGNA, M., PALMISANO, F., PATRUNO, C., NAPOLITANO, M., SCALVENZI, M. & AYALA, F. 2014. Psoriasis and sport: a new ally? *J Eur Acad Dermatol Venereol,* 30, 12607.

BARKER, J. N., JONES, M. L., MITRA, R. S., CROCKETT-TORABE, E., FANTONE, J. C., KUNKEL, S. L., WARREN, J. S., DIXIT, V. M. & NICKOLOFF, B. J. 1991. Modulation of keratinocyte-derived interleukin-8 which is chemotactic for neutrophils and T lymphocytes. *The American journal of pathology,* 139, 869.

BASRA, M. K. A., FENECH, R., GATT, R. M., SALEK, M. S. & FINLAY, A. Y. 2008. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *British Journal of Dermatology,* 159, 997-1035.

BAUR, D. M., CHRISTOPHI, C. A., COOK, E. F. & KALES, S. N. 2012. Age-Related Decline in Cardiorespiratory Fitness among Career Firefighters: Modification by Physical Activity and Adiposity. *Journal of Obesity,* 2012, 6.

BEINSBERGER, J., HEEMSKERK, J. W. & COSEMANS, J. M. 2014. Chronic arthritis and cardiovascular disease: altered blood parameters give rise to a prothrombotic propensity. *Semin Arthritis Rheum,* 44, 345-52.

BENJAMIN, E. J., LARSON, M. G., KEYES, M. J., MITCHELL, G. F., VASAN, R. S., KEANEY, J. F., LEHMAN, B. T., FAN, S., OSYPIUK, E. & VITA, J. A. 2004. Clinical Correlates and Heritability of Flow-Mediated Dilation in the Community: The Framingham Heart Study. *Circulation,* 109, 613-619.

BENSON, M. M. & FRISHMAN, W. H. 2015. The Heartbreak of Psoriasis: A Review of Cardiovascular Risk in Patients With Psoriasis. *Cardiology in Review,* 23, 312-316.

BEYGI, S., LAJEVARDI, V. & ABEDINI, R. 2014. C-reactive protein in psoriasis: a review of the literature. *Journal of the European Academy of Dermatology and Venereology,* 28, 700-711.

BLAAK, E. 2001. Gender differences in fat metabolism. *Curr Opin Clin Nutr Metab Care,* 4, 499-502.

BLACHER, J., GUERIN, A. P., PANNIER, B., MARCHAIS, S. J., SAFAR, M. E. & LONDON, G. M. 1999. Impact of Aortic Stiffness on Survival in End-Stage Renal Disease. *Circulation,* 99, 2434-2439.

BLOME, C., SIMIANER, S., PURWINS, S., LAASS, A., RUSTENBACH, S. J., SCHAEFER, I., RADTKE, M. & AUGUSTIN, M. 2010. Time needed for treatment is the major predictor of quality of life in psoriasis. *Dermatology (Basel, Switzerland),* 221, 154- 159.

BOEHNCKE, S., SALGO, R., GARBARAVICIENE, J., BESCHMANN, H., HARDT, K., DIEHL, S., FICHTLSCHERER, S., THACI, D. & BOEHNCKE, W. H. 2011a. Effective continuous systemic therapy of severe plaque-type psoriasis is accompanied by amelioration of biomarkers of cardiovascular risk: results of a prospective longitudinal observational study. *J Eur Acad Dermatol Venereol,* 25, 1187-93.

BOEHNCKE, S., THACI, D., BESCHMANN, H., LUDWIG, R. J., ACKERMANN, H., BADENHOOP, K. & BOEHNCKE, W. H. 2007a. Psoriasis patients show signs of insulin resistance. *Br J Dermatol,* 157, 1249-51.

BOEHNCKE, S., THACI, D., BESCHMANN, H., LUDWIG, R. J., ACKERMANN, H., BADENHOOP, K. & BOEHNCKE, W. H. 2007b. Psoriasis patients show signs of insulin resistance. *British Journal of Dermatology,* 157, 1249-1251.

BOEHNCKE, W.-H., BOEHNCKE, S., TOBIN, A.-M. & KIRBY, B. 2011b. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. *Experimental Dermatology,* 20, 303-307.

BOTH, H., ESSINK-BOT, M.-L., BUSSCHBACH, J. & NIJSTEN, T. 2007. Critical Review of Generic and Dermatology-Specific Health-Related Quality of Life Instruments. *J Invest Dermatol,* 127, 2726-2739.

BOUASSIDA, A., CHAMARI, K., ZAOUALI, M., FEKI, Y., ZBIDI, A. & TABKA, Z. 2008. Review on leptin and adiponectin responses and adaptations to acute and chronic exercise. *British Journal of Sports Medicine*.

BOUNDS, R. G., GRANDJEAN, P. W., O'BRIEN, B. C., INMAN, C. & CROUSE, S. F. 2000. Diet and short term plasma lipoprotein-lipid changes after exercise in trained Men. *Int J Sport Nutr Exerc Metab,* 10, 114-27.

BRUCE, K. D. & HANSON, M. A. 2010. The Developmental Origins, Mechanisms, and Implications of Metabolic Syndrome. *The Journal of Nutrition,* 140, 648-652.

BUGEON, L. & DALLMAN, M. J. 2000. Costimulation of T Cells. *American Journal of Respiratory and Critical Care Medicine,* 162, S164-S168.

BWEIR, S., AL-JARRAH, M., ALMALTY, A.-M., MAAYAH, M., SMIRNOVA, I. V., NOVIKOVA, L. & STEHNO-BITTEL, L. 2009. Resistance exercise training lowers HbA1C more than aerobic training in adults with type 2 diabetes. *Diabetology & Metabolic Syndrome,* 1, 27-27.

CALLEN, J. P., KRUEGER, G. G., LEBWOHL, M., MCBURNEY, E. I., MEASE, P., MENTER, A., PALLER, A. S., PARISER, D. M., WEINBLATT, M. & ZIMMERMAN, G. 2003. AAD consensus statement on psoriasis therapies*. *Journal of the American Academy of Dermatology,* 49, 897-899.

CAMERON, H., DAWE, R. S., YULE, S., MURPHY, J., IBBOTSON, S. H. & FERGUSON, J. 2002. A randomized, observer-blinded trial of twice vs. three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. *British Journal of Dermatology,* 147, 973-978.

CAMPA, M., MANSOURI, B., WARREN, R. & MENTER, A. 2016. A Review of Biologic Therapies Targeting IL-23 and IL-17 for Use in Moderate-to-Severe Plaque

Psoriasis. *Dermatology and Therapy,* 6, 1-12.

CARLQUIST, J. F., MUHLESTEIN, J. B. & ANDERSON, J. L. 2007. Lipoprotein-associated phospholipase A2: a new biomarker for cardiovascular risk assessment and potential therapeutic target. *Expert Rev Mol Diagn,* 7, 511-7.

CERMAN, A. A., BOZKURT, S., SAV, A., TULUNAY, A., ELBAŞı, M. O. & ERGUN, T. 2008. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. *British Journal of Dermatology,* 159, 820-826.

CHALMERS, R. J. G. 2015. Assessing Psoriasis Severity and Outcomes for Clinical Trials and Routine Clinical Practice. *Dermatologic Clinics,* 33, 57-71.

CHAO, D., FOY, C. G. & FARMER, D. 2000. Exercise Adherence among Older Adults: Challenges and Strategies. *Controlled Clinical Trials,* 21, S212-S217.

CHAUDHARI, U., ROMANO, P., MULCAHY, L. D., DOOLEY, L. T., BAKER, D. G. & GOTTLIEB, B. 2001. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *The Lancet,* 357, 1842-1847.

CHOW, C., SIMPSON, M. J., LUGER, T. A., CHUBB, H. & ELLIS, C. N. 2015. Comparison of three methods for measuring psoriasis severity in clinical studies (Part 1 of 2): change during therapy in Psoriasis Area and Severity Index, Static Physician's Global Assessment and Lattice System Physician's Global Assessment. *Journal of the European Academy of Dermatology and Venereology,* 29, 1406-1414.

CHULAROJANAMONTRI, L., GRIFFITHS, C. E. M. & CHALMERS, R. J. G. 2013. The Simplified Psoriasis Index (SPI): A Practical Tool for Assessing Psoriasis. *J Invest Dermatol,* 133, 1956-1962.

COHEN, A. D., SHERF, M., VIDAVSKY, L., VARDY, D. A., SHAPIRO, J. & MEYEROVITCH, J. 2008. Association between psoriasis and the metabolic syndrome. A cross-sectional study. *Dermatology,* 216, 152-5.

COIMBRA, S., CATARINO, C. & SANTOS-SILVA, A. 2016. The triad psoriasis-obesity-adipokine profile. *J Eur Acad Dermatol Venereol,* 27, 13701.

COIMBRA, S., FIGUEIREDO, A., CASTRO, E., ROCHA-PEREIRA, P. & SANTOS-SILVA, A. 2012. The roles of cells and cytokines in the pathogenesis of psoriasis. *International Journal of Dermatology,* 51, 389-398.

COIMBRA, S., OLIVEIRA, H., REIS, F., BELO, L., ROCHA, S., QUINTANILHA, A., FIGUEIREDO, A., TEIXEIRA, F., CASTRO, E., ROCHA-PEREIRA, P. & SANTOS-SILVA, A. 2009.

Circulating levels of adiponectin, oxidized LDL and C-reactive protein in Portuguese patients with psoriasis vulgaris, according to body mass index, severity and duration of the disease. *J Derm Sci,* 55, 202-204.

COIMBRA, S., OLIVEIRA, H., REIS, F., BELO, L., ROCHA, S., QUINTANILHA, A., FIGUEIREDO, A., TEIXEIRA, F., CASTRO, E., ROCHA-PEREIRA, P. & SANTOS-SILVA, A. 2010.

Circulating adipokine levels in Portuguese patients with psoriasis vulgaris according to body mass index, severity and therapy. *J Eur Acad Dermatol Venereol,* 24, 1386-94.

CORBETTA, S., ANGIONI, R., CATTANEO, A., BECK-PECCOZ, P. & SPADA, A. 2006. Effects of retinoid therapy on insulin sensitivity, lipid profile and circulating adipocytokines. *Eur J Endocrin,* 154, 83-6.

CRAIG, C. L., MARSHALL, A. L., SJOSTROM, M., BAUMAN, A. E., BOOTH, M. L., AINSWORTH, E., PRATT, M., EKELUND, U., YNGVE, A., SALLIS, J. F. & OJA, P. 2003. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc,* 35, 1381-95.

CRAIG, R. & MINDELL, J. 2013. Health Survey for England 2012. London: The Health and Social Care Information Centre

CUST, A. E., SMITH, B. J., CHAU, J., VAN DER PLOEG, H. P., FRIEDENREICH, C. M.,

ARMSTRONG, B. K. & BAUMAN, A. 2008. Validity and repeatability of the EPIC physical activity questionnaire: a validation study using accelerometers as an objective measure. ***International Journal of Behavioral Nutrition and Physical Activity,*** **5, 33.**

CZECH, W., SCHÖPE, E. & KAPP, A. 1996. Soluble E-selectin in sera of patients with atopic dermatitis and psoriasis—correlation with disease activity. ***British Journal of Dermatology,*** **134, 17-21.**

DAVIDOVICI, B. B., SATTAR, N., PRINZ, J. C., PUIG, L., EMERY, P., BARKER, J. N., VAN DE KERKHOF, P., STAHLE, M., NESTLE, F. O., GIROLOMONI, G. & KRUEGER, J. G. 2010.

Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. ***J Invest Dermatol,*** **130, 1785-96.**

DAWE, WAINWRIGHT, CAMERON & FERGUSON 1998. Narrow-band (TL-01) ultraviolet B phototherapy for chronic plaque psoriasis: three times or five times weekly treatment? ***British Journal of Dermatology,*** **138, 833-839.**

DEVRIMCI-OZGUVEN, H., KUNDAKCI, N., KUMBASAR, H. & BOYVAT, A. 2000. The depression, anxiety, life satisfaction and affective expression levels in psoriasis patients. ***Journal of the European Academy of Dermatology and Venereology,*** **14, 267-271.**

DIEFENBACH, M. A. & LEVENTHAL, H. 1996. The common-sense model of illness representation: Theoretical and practical considerations. ***Journal of social distress and the homeless,*** **5, 11-38.**

DI LERNIA, V., RICCI, C., LALLAS, A. & FICARELLI, E. 2014. Clinical predictors of non-response to any tumor necrosis factor (TNF) blockers: a retrospective study. ***Journal of Dermatological Treatment,*** **25, 73-74.**

DONAHUE, R. P., ZIMMET, P., BEAN, J. A., DECOURTEN, M., DONAHUE, R. A. D., COLLIER, G., GOLDBERG, R. B., PRINEAS, R. J., SKYLER, J. & SCHNEIDERMAN, N. 1999.

Cigarette Smoking, Alcohol Use, and Physical Activity in Relation to Serum Leptin Levels in a Multiethnic Population: The Miami Community Health Study. ***Annals of Epidemiology,*** **9, 108-113.**

DONG, J. & GOLDENBERG, G. 2017. New biologics in psoriasis: an update on IL-23 and IL-17 inhibitors. ***Cutis,*** **99, 123-127.**

DOWLATSHAHI, E. A., VAN DER VOORT, E. A. M., ARENDS, L. R. & NIJSTEN, T. 2013. Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. ***British Journal of Dermatology,*** **169, 266-282.**

DYRSTAD, S. M., HANSEN, B. H., HOLME, I. M. & ANDERSSEN, S. A. 2014. Comparison of self-reported versus accelerometer-measured physical activity. ***Med Sci Sports Exerc,*** **46, 99-106.**

ECKEL, R. H., GRUNDY, S. M. & ZIMMET, P. Z. 2005. The metabolic syndrome. ***The Lancet,*** **365, 1415-1428.**

EGEBERG, A., HANSEN, P. R., GISLASON, G. H., SKOV, L. & MALLBRIS, L. 2016. Risk of self-harm and nonfatal suicide attempts, and completed suicide in patients with psoriasis: a population-based cohort study. ***Br J Dermatol,*** **175, 493-500.**

EMKEN, B. A., RICHEY, J., BELCHER, B., HSU, Y.-W. & SPRUIJT-METZ, D. 2010. Objectively Measured Physical Activity Is Negatively Associated with Plasma Adiponectin Levels in Minority Female Youth. ***International Journal of Pediatric Endocrinology,*** **2010, 846070.**

FANG, C., LEI, J., ZHOU, S. X., ZHANG, Y. L., YUAN, G. Y. & WANG, J. F. 2013. Association of higher resistin levels with inflammatory activation and endothelial dysfunction in patients with essential hypertension. ***Chin Med J,*** **126, 646-9.**

FANTUZZI, G. 2008. Adiponectin and inflammation: consensus and controversy. ***J Allergy***

Clin Immunol, 121, 326-30.

FELDMAN, S. R., FLEISCHER, A. B., JR., REBOUSSIN, D. M., RAPP, S. R., EXUM, M. L., CLARK, A. R. & NURRE, L. 1996. The Self-Administered Psoriasis Area and Severity Index Is Valid and Reliable. *J Investig Dermatol,* 106, 183-186.

FELDMAN, S. R. & KRUEGER, G. G. 2005. Psoriasis assessment tools in clinical trials. *Annals of the Rheumatic Diseases,* 64, ii65-ii68.

FINLAY, A. Y. 2005. Current severe psoriasis and the Rule of Tens. *British Journal of Dermatology,* 152, 861-867.

FINLAY, A. Y. & KHAN, G. K. 1994. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clinical and Experimental Dermatology,* 19, 210- 216.

FINUCANE, M. M., STEVENS, G. A., COWAN, M. J., DANAEI, G., LIN, J. K., PACIOREK, C. J., SINGH, G. M., GUTIERREZ, H. R., LU, Y., BAHALIM, A. N., FARZADFAR, F., RILEY, L. M. & EZZATI, M. 2011. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *The Lancet,* 377, 557- 567.

FITZGERALD, R., SADLIER, M., CONNOLLY, M. & TOBIN, A. M. 2014. Psoriasis and insulin resistance: a review. *Journal of Diabetes Research and Clinical Metabolism,* 3.

FLEG, J. L., MORRELL, C. H., BOS, A. G., BRANT, L. J., TALBOT, L. A., WRIGHT, J. G. & LAKATTA, E. G. 2005. Accelerated Longitudinal Decline of Aerobic Capacity in Healthy Older Adults. *Circulation,* 112, 674.

FLEISCHER, A. B., JR., RAPP, S. R., REBOUSSIN, D. M., VANARTHOS, J. C. & FELDMAN, S. R. 1994. Patient Measurement of Psoriasis Disease Severity with a Structured Instrument. *J Investig Dermatol,* 102, 967-969.

FLEMING, I. & BUSSE, R. 2003. Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology,* 284, R1-R12.

FORTES, C., MASTROENI, S., LEFFONDRÉ, K., SAMPOGNA, F., MELCHI, F., MAZZOTTI, E., PASQUINI, P. & ABENI, D. 2005. Relationship between smoking and the clinical severity of psoriasis. *Archives of Dermatology,* 141, 1580-1584.

FORTUNE, D. G., MAIN, C. J., O'SULLIVAN, T. M. & GRIFFITHS, C. E. M. 1997a. Assessing illness-related stress in psoriasis: The psychometric properties of the Psoriasis Life Stress Inventory. *Journal of Psychosomatic Research,* 42, 467-475.

FORTUNE, D. G., MAIN, C. J., O'SULLIVAN, T. M. & GRIFFITHS, C. E. M. 1997b. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis- specific stress. *British Journal of Dermatology,* 137, 755-760.

FORTUNE, D. G., RICHARDS, H. L., CORRIN, A., TAYLOR, R. J., GRIFFITHS, C. E. M. & MAIN, C. J. 2003. Attentional bias for psoriasis-specific and psychosocial threat in patients with psoriasis. *Journal of behavioral medicine,* 26, 211-224.

FORTUNE, D. G., RICHARDS, H. L. & GRIFFITHS, C. E. M. 2005. Psychologic Factors in Psoriasis: Consequences, Mechanisms, and Interventions. *Dermatologic Clinics,* 23, 681-694.

FORTUNE, D. G., RICHARDS, H. L., KIRBY, B., BOWCOCK, S., MAIN, C. J. & GRIFFITHS, C. E. M. 2002. A cognitive-behavioural symptom management programme as an adjunct in psoriasis therapy. *British Journal of Dermatology,* 146, 458-465.

FORTUNE, D. G., RICHARDS, H. L., MAIN, C. J. & GRIFFITHS, C. E. M. 2000. Pathological worrying, illness perceptions and disease severity in patients with psoriasis. *British Journal of Health Psychology,* 5, 71-82.

FRANCOIS, M. E. & LITTLE, J. P. 2015. Effectiveness and Safety of High-Intensity Interval Training in Patients With Type 2 Diabetes. *Diabetes Spectrum,* 28, 39-44.

FRANKEL, H. C., HAN, J. L. T. & QURESHI, A. A. 2012. THe association between physical activity and the risk of incident psoriasis. *Archives of Dermatology,* 148, 918-

924.
FREDRIKSSON, T. & PETTERSSON, U. 1978. Severe psoriasis–oral therapy with a new retinoid. *Dermatology,* 157, 238-244.
FREIMAN, A., BIRD, G., METELITSA, A., BARANKIN, B. & LAUZON, G. 2004. Cutaneous Effects of Smoking. *Journal of Cutaneous Medicine and Surgery,* 8, 415-423.
FROSTEGÅRD, J. 2013. Immunity, atherosclerosis and cardiovascular disease. *BMC Medicine,* 11, 1-13.
FROSTEGARD, J., ULFGREN, A. K., NYBERG, P., HEDIN, U., SWEDENBORG, J., ANDERSSON, U. & HANSSON, G. K. 1999. Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage- stimulating cytokines. *Atherosclerosis,* 145, 33-43.
FRY, L. 1988. Psoriasis. *British Journal of Dermatology,* 119, 445-461.
FRY, L. & BAKER, B. S. 2007. Triggering psoriasis: the role of infections and medications. *Clinics in Dermatology,* 25, 606-615.
GARBER, C. E., BLISSMER, B., DESCHENES, M. R., FRANKLIN, B., LAMONTE, M. J., LEE, I.-M., NIEMAN, D. C. & SWAIN, D. P. 2011. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise,* 43, 1334-1359.
GARCIA-PEREZ, M. E., STEVANOVIC, T. & POUBELLE, P. E. 2013. New therapies under development for psoriasis treatment. *Curr Opin Pediatr,* 25, 480-7.
GASPARI, A. A. 2006. Innate and adaptive immunity and the pathophysiology of psoriasis. *Journal of the American Academy of Dermatology,* 54, S67-S80.
GELFAND, J. M., NEIMANN, A. L., SHIN, D. B., WANG, X., MARGOLIS, D. J. & TROXEL, A. B. 2006. Risk of myocardial infarction in patients with psoriasis. *JAMA,* 296, 1735- 1741.
GERDES, S., OSADTSCHY, S., ROSTAMI-YAZDI, M., BUHLES, N., WEICHENTHAL, M. & MROWIETZ, U. 2012. Leptin, adiponectin, visfatin and retinol-binding protein-4 – mediators of comorbidities in patients with psoriasis? *Experimental Dermatology,* 21, 43-47.
GERDES, S., ZAHL, V. A., WEICHENTHAL, M. & MROWIETZ, U. 2010. Smoking and Alcohol Intake in Severely Affected Patients with Psoriasis in Germany. *Dermatology,* 220, 38-43.
GHAFOURIAN, M., ASHTARY-LARKY, D., CHINIPARDAZ, R., ESKANDARY, N. & MEHAVARAN, M. 2016. Inflammatory Biomarkers' Response to Two Different Intensities of a Single Bout Exercise Among Soccer Players. *Iranian Red Crescent Medical Journal,* 18, e21498.
GHAZIZADEH, R., TOSA, M. & GHAZIZADEH, M. 2011. Clinical Improvement in Psoriasis With Treatment of Associated Hyperlipidemia. *The American Journal of the Medical Sciences,* 341.
GHORESCHI, K., WEIGERT, C. & RÖCKEN, M. 2007. Immunopathogenesis and role of T cells in psoriasis. *Clinics in Dermatology,* 25, 574-580.
GINSBURG, I. H. & LINK, B. G. 1989. Feelings of stigmatization in patients with psoriasis. *Journal of the American Academy of Dermatology,* 20, 53-63.
GISONDI, P., DEL GIGLIO, M., DI FRANCESCO, V., ZAMBONI, M. & GIROLOMONI, G. 2008a. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. *The American Journal of Clinical Nutrition,* 88, 1242-1247.
GISONDI, P., FANTIN, F., DEL GIGLIO, M., VALBUSA, F., MARINO, F., ZAMBONI, M. & GIROLOMONI, G. 2008b. Chronic Plaque Psoriasis Is Associated with Increased Arterial Stiffness. *Dermatology,* 218, 110-113.
GISONDI, P., TESSARI, G., CONTI, A., PIASERICO, S., SCHIANCHI, S., PESERICO, A.,

GIANNETTI, A. & GIROLOMONI, G. 2007. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case–control study. *British Journal of Dermatology,* 157, 68-73.

GNIADECKI, R., ROBERTSON, D., MOLTA, C. T., FREUNDLICH, B., PEDERSEN, R., LI, W., BOGGS, R. & ZBROZEK, A. S. 2012. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *Journal of the European Academy of Dermatology and Venereology,* 26, 1436-1443.

GOLBIDI, S. & LAHER, I. 2012. Exercise and the Cardiovascular System *Cardiology Research and Practice* 2012, 15.

GOLDHAMMER, E., TANCHILEVITCH, A., MAOR, I., BENIAMINI, Y., ROSENSCHEIN, U. & SAGIV, M. 2005. Exercise training modulates cytokines activity in coronary heart disease patients. *International Journal of Cardiology,* 100, 93-99.

GOMEZ-MERINO, D., CHENNAOUI, M., DROGOU, C., BONNEAU, D. & GUEZENNEC, C. Y. 2002. Decrease in serum leptin after prolonged physical activity in men. *Medicine and science in sports and exercise,* 34, 1594-1599.

GONZÁLEZ-GAY, M. A., GONZÁLEZ-VELA, C. & GONZÁLEZ-JUANATEY, C. 2012. Psoriasis: a Skin Disease Associated With Increased Cardiovascular Risk. *Actas Dermo- Sifiliográficas (English Edition),* 103, 595-598.

GOTTLIEB, A. B., CHAO, C. & DANN, F. 2008. Psoriasis comorbidities. *Journal of Dermatological Treatment,* 19, 5-21.

GRANDJEAN, P. W., CROUSE, S. F. & ROHACK, J. J. 2000. Influence of cholesterol status on blood lipid and lipoprotein enzyme responses to aerobic exercise. *J Appl Physiol (1985),* 89, 472-80.

GRIFFITHS, C. E.M. & BARKER, J. N. 2007. Pathogenesis and clinical features of psoriasis. *Lancet,* 370, 263-271.

GRIFFITHS, C. E. M. 1990. Systemic and local administration of cyclosporine in the treatment of psoriasis. *Journal of the American Academy of Dermatology,* 23, 1242-1247.

GRIFFITHS, C. E. M. 2003. The immunological basis of psoriasis. *Journal of the European Academy of Dermatology and Venereology,* 17, 1-5.

GRIFFITHS, C. E. M., CHRISTOPHERS, E., BARKER, J. N. W. N., CHALMERS, R. J. G., CHIMENTI, S., KRUEGER, G. G., LEONARDI, C., MENTER, A., ORTONNE, J. P. & FRY, L. 2007. A classification of psoriasis vulgaris according to phenotype. *British Journal of Dermatology,* 156, 258-262.

GRIFFITHS, C. E. M. & RICHARDS, H. L. 2001. Psychological influences in psoriasis. *Clinical and Experimental Dermatology,* 26, 338-342.

GROVES, R. W., KAPAHI, P., BARKER, J. N., HASKARD, D. O. & MACDONALD, D. M. 1995. Detection of circulating adhesion molecules in erythrodermic skin disease. *J Am Acad Dermatol,* 32, 32-6.

GU, J.-W., GADONSKI, G., WANG, J., MAKEY, I. & ADAIR, T. 2004. Exercise increases endostatin in circulation of healthy volunteers. *BMC Physiology,* 4, 2.

GUPTA 1998. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *British Journal of Dermatology,* 139, 846- 850.

GUPTA, M. A. & GUPTA, A. K. 1995. AGE AND GENDER DIFFERENCES IN THE IMPACT OF PSORIASIS ON QUALITY OF LIFE. *International Journal of Dermatology,* 34, 700-703. GUPTA, M. A. & GUPTA, A. K. 2003. Psychiatric and Psychological Co-Morbidity in Patients with Dermatologic Disorders: Epidemiology and Management. *American Journal of Clinical Dermatology,* 4, 833-842.

GUPTA, M. A., SCHORK, N. J., GUPTA, A. K., KIRKBY, S. & ELLIS, C. N. 1993. SUICIDAL

IDEATION IN PSORIASIS. *International Journal of Dermatology,* 32, 188-190.

GUTTMAN-YASSKY, E., LOWES, M. A., FUENTES-DUCULAN, J., ZABA, L. C., CARDINALE, I., NOGRALES, K. E., KHATCHERIAN, A., NOVITSKAYA, I., CARUCCI, J. A., BERGMAN, R.

& KRUEGER, J. G. 2008. Low Expression of the IL-23/Th17 Pathway in Atopic Dermatitis Compared to Psoriasis. *The Journal of Immunology,* 181, 7420-7427.

HAGSTROMER, M., AINSWORTH, B. E., OJA, P. & SJOSTROM, M. 2010. Comparison of a subjective and an objective measure of physical activity in a population sample. *Journal of physical activity & health,* 7, 541.

HAKOLA, L., KOMULAINEN, P., HASSINEN, M., SAVONEN, K., LITMANEN, H., LAKKA, T. A. &

RAURAMAA, R. 2011. Cardiorespiratory fitness in aging men and women: the DR's EXTRA study. *Scandinavian Journal of Medicine & Science in Sports,* 21, 679-687.

HALLAJI, Z., BARZEGARI, M., BALIGHI, K., MANSOORI, P., TAHERI, A. & MANSOORI, P. 2010. A comparison of three times vs. five times weekly narrowband ultraviolet B phototherapy for the treatment of chronic plaque psoriasis. *Photodermatology, Photoimmunology & Photomedicine,* 26, 10-15.

HAMBRECHT, R., FIEHN, E., WEIGL, C., GIELEN, S., HAMANN, C., KAISER, R., YU, J., ADAMS,

V., NIEBAUER, J. & SCHULER, G. 1998. Regular Physical Exercise Corrects Endothelial Dysfunction and Improves Exercise Capacity in Patients With Chronic Heart Failure. *Circulation,* 98, 2709-2715.

HAMMINGA, E. A., VAN DER LELY, A. J., NEUMANN, H. A. & THIO, H. B. 2006. Chronic

inflammation in psoriasis and obesity: implications for therapy. *Medical hypotheses,* 67, 768-773.

HASKELL, W. L., LEE, I. M., PATE, R. R., POWELL, K. E., BLAIR, S. N., FRANKLIN, B. A., MACERA, C. A., HEATH, G. W., THOMPSON, P. D. & BAUMAN, A. 2007. Physical

activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation,* 116, 1081.

HASKELL, W. L., SIMS, C., MYLL, J., BORTZ, W. M., ST GOAR, F. G. & ALDERMAN, E. L. 1993.

Coronary artery size and dilating capacity in ultradistance runners. *Circulation,* 87, 1076-1082.

HASKELL, W. L., TAYLOR, H. L., WOOD, P. D., SCHROTT, H. & HEISS, G. 1980. Strenuous

physical activity, treadmill exercise test performance and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program Prevalence Study. *Circulation,* 62, IV53-61.

HAYES, J. & KOO, J. 2010. Psoriasis: depression, anxiety, smoking, and drinking habits. *Dermatologic Therapy,* 23, 174-180.

HEIN, H. O., SUADICANI, P. & GYNTELBERG, F. 1992. Physical fitness or physical activity as a predictor of ischaemic heart disease? A 17-year follow-up in the Copenhagen Male Study. *Journal of Internal Medicine,* 232, 471-479.

HENSELER, T. & CHRISTOPHERS, E. 1985. Psoriasis of early and late onset: Characterization of two types of psoriasis vulgaris. *Journal of the American Academy of Dermatology,* 13, 450-456.

HENSELER, T. & SCHMITT-RAU, K. 2008. A comparison between BSA, PASI, PLASI and SAPASI as measures of disease severity and improvement by therapy in patients with psoriasis. *International Journal of Dermatology,* 47, 1019-1023.

HERRON, M., HINCKLEY, M. & HOFFMAN, M. S. 2005. Impact of obesity and smoking on psoriasis presentation and management. *Archives of Dermatology,* 141, 1527- 1534.

HIGGINS 2000. Alcohol, smoking and psoriasis. *Clinical and Experimental Dermatology,* 25, 107-110.

HODULIK, S. G. & ZEICHNER, J. A. 2006. Combination therapy with acitretin for psoriasis. ***Journal of Dermatological Treatment,*** **17, 108-111.**

HORREAU, C., POUPLARD, C., BRENAUT, E., BARNETCHE, T., MISERY, L., CRIBIER, B., JULLIEN, D., ARACTINGI, S., AUBIN, F., JOLY, P., LE MAITRE, M., ORTONNE, J. P.,

PAUL, C. & RICHARD, M. A. 2013. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. ***J Eur Acad Dermatol Venereol,*** **3, 12-29.**

HUANG, Y. H., YANG, L. C., HUI, R.-Y., CHANG, Y. C., YANG, Y. W., YANG, C. H., CHEN, Y. H.,

CHUNG, W. H., KUAN, Y. Z. & CHIU, C. S. 2010. Relationships between obesity and the clinical severity of psoriasis in Taiwan. ***Journal of the European Academy of Dermatology and Venereology,*** **24, 1035-1039.**

HUTTUNEN, J. K., LÄNSIMIES, E., VOUTILAINEN, E., EHNHOLM, C., HIETANEN, E., PENTTILÄ,

I., SIITONEN, O. & RAURAMAA, R. 1979. Effect of moderate physical exercise on serum lipoproteins. A controlled clinical trial with special reference to serum high-density lipoproteins. ***Circulation,*** **60, 1220-1229.**

HUYBRECHTS, S. A., DEVOS, D. G., VERMEERSCH, S. J., MAHIEU, D., ACHTEN, E., DE BACKER,

T. L., SEGERS, P. & VAN BORTEL, L. M. 2011. Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path lengths determined by MRI and superficial measurements. ***J Hypertens,*** **29, 1577-82.**

HWANG, S.-J., BALLANTYNE, C. M., SHARRETT, A. R., SMITH, L. C., DAVIS, C. E., GOTTO, A.

M. & BOERWINKLE, E. 1997. Circulating Adhesion Molecules VCAM-1, ICAM-1, and E-selectin in Carotid Atherosclerosis and Incident Coronary Heart Disease Cases: The Atherosclerosis Risk In Communities (ARIC) Study. ***Circulation,*** **96, 4219-4225.**

IKONOMIDIS, I., MAKAVOS, G. & LEKAKIS, J. 2015a. Arterial stiffness and coronary artery disease. ***Curr Opin Cardiol,*** **30, 422-31.**

IKONOMIDIS, I., MAKAVOS, G., PAPADAVID, E., VAROUDI, M., ANDREADOU, I., GRAVANIS, K., THEODOROPOULOS, K., PAVLIDIS, G., TRIANTAFYLLIDI, H., PARISSIS, J.,

PARASKEVAIDIS, I., RIGOPOULOS, D. & LEKAKIS, J. 2015b. Similarities in Coronary Function and Myocardial Deformation Between Psoriasis and Coronary Artery Disease: The Role of Oxidative Stress and Inflammation. ***Canadian Journal of Cardiology,*** **31, 287-295.**

INGELSSON, E., HULTHE, J. & LIND, L. 2008. Inflammatory markers in relation to insulin resistance and the metabolic syndrome. ***Eur J Clin Invest,*** **38, 502-9.**

INGRAM, D. K. 2000. Age-related decline in physical activity: generalization to nonhumans. ***Medicine and science in sports and exercise,*** **32, 1623-1629.**

ISHIHARA, K. & HIRANO, T. 2002. IL-6 in autoimmune disease and chronic inflammatory proliferative disease. ***Cytokine & Growth Factor Reviews,*** **13, 357-368.**

JALALY, L., SHARIFI, G., FARAMARZI, M., NEMATOLLAHI, A., RAFIEIAN-KOPAEI, M., AMIRI,

M. & MOATTAR, F. 2015. Comparison of the effects of Crataegus oxyacantha extract, aerobic exercise and their combination on the serum levels of ICAM-1 and E-Selectin in patients with stable angina pectoris. ***DARU Journal of Pharmaceutical Sciences,*** **23, 54.**

JOHNSTON, A., ARNADOTTIR, S., GUDJONSSON, J. E., APHALE, A., SIGMARSDOTTIR, A. A., GUNNARSSON, S. I., STEINSSON, J. T., ELDER, J. T. & VALDIMARSSON, H. 2008.

Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. ***Br J Dermatol,*** **159, 342-50.**

KADOGLOU, N. P., PERREA, D., ILIADIS, F., ANGELOPOULOU, N., LIAPIS, C. & ALEVIZOS, M.

2007. Exercise Reduces Resistin and Inflammatory Cytokines in Patients With Type 2

Diabetes. *Diabetes Care,* 30, 719-721.
KADOWAKI, T., YAMAUCHI, T., KUBOTA, N., HARA, K., UEKI, K. & TOBE, K. 2006. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *Journal of Clinical Investigation,* 116, 1784-1792.
KARADAG, A. S., YAVUZ, B., ERTUGRUL, D. T., AKIN, K. O., YALCIN, A. A., DEVECI, O. S., ATA, N., KUCUKAZMAN, M. & DAL, K. 2010. Is psoriasis a pre-atherosclerotic disease? Increased insulin resistance and impaired endothelial function in patients with psoriasis. *International Journal of Dermatology,* 49, 642-646.
KASAPIS, C. & THOMPSON, P. D. 2005. The Effects of Physical Activity on Serum C-Reactive Protein and Inflammatory MarkersA Systematic Review. *Journal of the American College of Cardiology,* 45, 1563-1569.
KAUR, S., ZILMER, K., LEPING, V. & ZILMER, M. 2011. The levels of adiponectin and leptin and their relation to other markers of cardiovascular risk in patients with psoriasis. *Journal of the European Academy of Dermatology and Venereology,* 25, 1328- 1333.
KAVAZIS, A. N., MCCLUNG, J. M., HOOD, D. A. & POWERS, S. K. 2008. Exercise induces a cardiac mitochondrial phenotype that resists apoptotic stimuli. *American Journal of Physiology - Heart and Circulatory Physiology,* 294, H928-H935.
KEYWORTH, C., NELSON, P. A., GRIFFITHS, C. E. M., CORDINGLEY, L. & BUNDY, C. 2015. Do English healthcare settings use 'Choice Architecture'principles in promoting healthy lifestyles for people with psoriasis? An observational study. *BMC health services research,* 15, 1.
KHOURY, L. R., DANIELSEN, P. L. & SKIVEREN, J. 2014. Body image altered by psoriasis. A study based on individual interviews and a model for body image. *J Dermatolog Treat,* 25, 2-7.
KILIC, A. & GUL, U. 2010. Treatment Options for Patients with Psoriasis. *European Dermatology* 5, 16-21.
KIMBALL, A. B., GIELER, U., LINDER, D., SAMPOGNA, F., WARREN, R. B. & AUGUSTIN, M. 2010a. Psoriasis: is the impairment to a patient's life cumulative? *Journal of the European Academy of Dermatology and Venereology,* 24, 989-1004.
KIMBALL, A. B., GLADMAN, D., GELFAND, J. M., GORDON, K., HORN, E. J., KORMAN, N. J., KORVER, G., KRUEGER, G. G., STROBER, B. E. & LEBWOHL, M. G. 2008. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *Journal of the American Academy of Dermatology,* 58, 1031-1042.
KIMBALL, A. B., GUERIN, A., LATREMOUILLE-VIAU, D., YU, A. P., GUPTA, S., BAO, Y. & MULANI, P. 2010b. Coronary Heart Disease and Stroke Risk in Patients with Psoriasis: Retrospective Analysis. *The American Journal of Medicine,* 123, 350-357.
KIRBY, B., FORTUNE, D. G., BHUSHAN, M., CHALMERS, R. J. G. & GRIFFITHS, C. E. M. 2000. The Salford Psoriasis Index: an holistic measure of psoriasis severity. *British Journal of Dermatology,* 142, 728-732.
KIRBY, B., RICHARDS, H. L., MASON, D. L., FORTUNE, D. G., MAIN, C. J. & GRIFFITHS, C. E. M. 2008. Alcohol consumption and psychological distress in patients with psoriasis. *British Journal of Dermatology,* 158, 138-140.
KIRBY, B., RICHARDS, H. L., WOO, P., HINDLE, E., MAIN, C. J. & GRIFFITHS, C. E. 2001. Physical and psychologic measures are necessary to assess overall psoriasis severity. *Journal of the American Academy of Dermatology,* 45, 72-76.
KITCHEN, H., CORDINGLEY, L., YOUNG, H., GRIFFITHS, C. E. M. & BUNDY, C. 2015. Patient-reported outcome measures in psoriasis: the good, the bad and the missing! *British Journal of Dermatology,* 172, 1210-1221.
KLEYN, C. E., MCKIE, S., ROSS, A. R., MONTALDI, D., GREGORY, L. J., ELLIOTT, R., ISAACS, C.

L., ANDERSON, I. M., RICHARDS, H. L., DEAKIN, J. F., FORTUNE, D. G. & GRIFFITHS, C. E. 2009. Diminished neural and cognitive responses to facial expressions of disgust in patients with psoriasis: a functional magnetic resonance imaging study. *J Invest Dermatol,* 129, 2613-9.

KÖLLIKER FRERS, R. A., BISOENDIAL, R. J., MONTOYA, S. F., KERZKERG, E., CASTILLA, R., TAK, P. P., MILEI, J. & CAPANI, F. 2015. Psoriasis and cardiovascular risk: Immune- mediated crosstalk between metabolic, vascular and autoimmune inflammation. *IJC Metabolic & Endocrine,* 6, 43-54.

KONDO, T., KOBAYASHI, I. & MURAKAMI, M. 2006. Effect of exercise on circulating adipokine levels in obese young women. *Endocr J,* 53, 189-95.

KOO, J. & NAKAMURA, M. 2017. PUVA for the Treatment of Moderate to Severe Psoriasis. *Clinical Cases in Phototherapy.* Springer.

KURD, S. K., TROXEL, A. B., CRITS-CHRISTOPH, P. & GELFAND, J. M. 2010. The risk of depression, anxiety and suicidality in patients with psoriasis: A population-based cohort study. *Archives of Dermatology,* 146, 891-895.

KURWA, H. & FINLAY, A. Y. 1995. Dermatology in-patient management greatly improves life quality. *British Journal of Dermatology,* 133, 575-578.

LALLY, P., VAN JAARSVELD, C. H., POTTS, H. W. & WARDLE, J. 2010. How are habits formed: Modelling habit formation in the real world. *European journal of social psychology,* 40, 998-1009.

LANGLEY, R. G. & ELLIS, C. N. 2004. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *Journal of the American Academy of Dermatology,* 51, 563-569.

LANGLEY, R. G. B., KRUEGER, G. G. & GRIFFITHS, C. E. M. 2005. Psoriasis: epidemiology, clinical features, and quality of life. *Annals of the Rheumatic Diseases,* 64, ii18-ii23.

LAURENT, S., COCKCROFT, J., VAN BORTEL, L., BOUTOUYRIE, P., GIANNATTASIO, C., HAYOZ, D., PANNIER, B., VLACHOPOULOS, C., WILKINSON, I. & STRUIJKER-BOUDIER, H. 2006. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *European Heart Journal,* 27, 2588-2605.

LAWS, P. M. & YOUNG, H. S. 2010. Topical treatment of psoriasis. *Expert Opinion on Pharmacotherapy,* 11, 1999-2009.

LAWS, P. M., YOUNG, H. S. & WARREN, R. B. unpublished. Psoriasis and Comorbidities. *Advances in Psoriasis (Weinberg J, Lebwohl M, eds). New York, USA. Springer (in press)*.

LEBWOHL, M. & ALI, S. 2001. Treatment of psoriasis. Part 2. Systemic therapies. *Journal of the American Academy of Dermatology,* 45, 649-661.

LEE, M. C., CHEN, Y. C., HO, G. J., SHIH, M. H., CHOU, K. C. & HSU, B. G. 2014. Serum Leptin Levels Positively Correlate With Peripheral Arterial Stiffness in Kidney Transplantation Patients. *Transplantation Proceedings,* 46, 353-358.

LEE, P. H., MACFARLANE, D. J., LAM, T. H. & STEWART, S. M. 2011. Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic. *International Journal of Behavioral Nutrition and Physical Activity,* 8, 115.

LEE, R. & HO, A. 2012. Physical Activity and Socioeconomic Status. *In:* MOOREN, F. (ed.) *Encyclopedia of Exercise Medicine in Health and Disease.* Springer Berlin Heidelberg.

LEIBOWITZ, E., SEIDMAN, D., LAOR, A., SHAPIRO, Y. & EPSTEIN, Y. 1991. Are psoriatic patients at risk of heat intolerance? *British journal of dermatology,* 124, 439-442.

LEINO, M., MUSTONEN, A., MATTILA, K., KOULU, L. & TUOMINEN, R. 2014. Perceived impact of psoriasis on leisure-time activities. *European Journal of Dermatology,* 24, 224-228.

LEWIS, V. J. & FINLAY, A. Y. 2005. Two decades experience of the Psoriasis Disability Index. *Dermatology,* 210, 261-268.

LIBBY, P. 2006. Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr,* 83, 456S-460S.

LIN, T. Y., SEE, L. C., SHEN, Y. M., LIANG, C. Y., CHANG, H. N. & LIN, Y. K. 2011. Quality of life in patients with psoriasis in northern Taiwan. *Chang Gung Med J,* 34, 186-96.

LIN, V. W. 2012. Tough-Skinned Kids: Identifying Psychosocial Effects of Psoriasis and Helping Pediatric Patients and Families Cope. *Journal of Pediatric Nursing,* 27, 563- 572.

LIU, D., FERNANDEZ, B. O., HAMILTON, A., LANG, N. N., GALLAGHER, J. M. C., NEWBY, D. E., FEELISCH, M. & WELLER, R. B. 2014. UVA Irradiation of Human Skin Vasodilates Arterial Vasculature and Lowers Blood Pressure Independently of Nitric Oxide Synthase. *Journal of Investigative Dermatology,* 134, 1839-1846.

LONNBERG, A. S., SKOV, L., SKYTTHE, A., KYVIK, K. O., PEDERSEN, O. B. & THOMSEN, S. F. 2016. Smoking and risk for psoriasis: a population-based twin study. *Int J Dermatol,* 55, e72-8.

LONG, J. W., TAO, J., PI, X. M., WANG, Y. Y. & TU, Y. T. 2010. Effect of narrow-band UVB phototherapy on soluble cell adhesion molecules in patients with psoriasis vulgaris. *J Int Med Res,* 38, 1507-12.

LOWES, M. A., BOWCOCK, A. M. & KRUEGER, J. G. 2007. Pathogenesis and therapy of psoriasis. *Nature,* 445, 866-873.

LOWES, M. A., KIKUCHI, T., FUENTES-DUCULAN, J., CARDINALE, I., ZABA, L. C., HAIDER, A. S., BOWMAN, E. P. & KRUEGER, J. G. 2008. Psoriasis Vulgaris Lesions Contain Discrete Populations of Th1 and Th17 T Cells. *J Invest Dermatol,* 128, 1207-1211.

LUI, H. & MAMELAK, A. 2011. Plaque psoriasis. *Medscape, Mar*.

MA, C., HARSKAMP, C. T., ARMSTRONG, E. J. & ARMSTRONG, A. W. 2013. The association between psoriasis and dyslipidaemia: a systematic review. *British Journal of Dermatology,* 168, 486-495.

MACKENZIE, I. S., WILKINSON, I. B. & COCKCROFT, J. R. 2002. Assessment of arterial stiffness in clinical practice. *QJM,* 95, 67-74.

MADANAGOBALANE, S., SANDHYA, V., ANANDAN, S. & SESHADRI, K. G. 2014. Circulating adiponectin levels in Indian patients with psoriasis and its relation to metabolic syndrome. *Indian Journal of Endocrinology and Metabolism,* 18, 191-196.

MAHMUD, A. & FEELY, J. 2005a. Adiponectin and Arterial Stiffness. *American Journal of Hypertension,* 18, 1543-1548.

MAHMUD, A. & FEELY, J. 2005b. Arterial Stiffness Is Related to Systemic Inflammation in Essential Hypertension. *Hypertension,* 46, 1118-1122.

MALLBRIS, L., AKRE, O., GRANATH, F., YIN, L., LINDELÖF, B., EKBOM, A. & STÅHLE-BÄCKDAHL, M. 2004. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *European journal of epidemiology,* 19, 225-230. MANCIA, G., FAGARD, R., NARKIEWICZ, K., REDON, J., ZANCHETTI, A., BÖHM, M., CHRISTIAENS, T., CIFKOVA, R., DE BACKER, G., DOMINICZAK, A., GALDERISI, M., GROBBEE, D. E., JAARSMA, T., KIRCHHOF, P., KJELDSEN, S. E., LAURENT, S., MANOLIS, A. J., NILSSON, P. M., RUILOPE, L. M., SCHMIEDER, R. E., SIRNES, P. A., SLEIGHT, P., VIIGIMAA, M., WAEBER, B., ZANNAD, F., REDON, J., DOMINICZAK, A., NARKIEWICZ, K., NILSSON, P. M., BURNIER, M., VIIGIMAA, M., AMBROSIONI, E., CAUFIELD, M., COCA, A., OLSEN, M. H., SCHMIEDER, R. E., TSIOUFIS, C., VAN DE BORNE, P., ZAMORANO, J. L., ACHENBACH, S., BAUMGARTNER, H., BAX, J. J., BUENO, H., DEAN, V., DEATON, C., EROL, C., FAGARD, R., FERRARI, R., HASDAI, D.,HOES, A. W., KIRCHHOF, P., KNUUTI, J., KOLH, P., LANCELLOTTI, P., LINHART, A., NIHOYANNOPOULOS, P., PIEPOLI, M. F., PONIKOWSKI, P., SIRNES, P. A., TAMARGO, J. L., TENDERA, M., TORBICKI, A., WIJNS, W., WINDECKER, S., CLEMENT, D. L., COCA, A., GILLEBERT, T. C., TENDERA, M., ROSEI, E. A.,

AMBROSIONI, E., ANKER, S. D., BAUERSACHS, J., HITIJ, J. B., CAULFIELD, M., DE BUYZERE, M., DE GEEST, S., DERUMEAUX, G. A., ERDINE, S., FARSANG, C., FUNCK-BRENTANO, C., GERC, V., GERMANO, G., GIELEN, S., HALLER, H., HOES, A. W., JORDAN, J., KAHAN, T., KOMAJDA, M., LOVIC, D., MAHRHOLDT, H., OLSEN, M. H., OSTERGREN, J., PARATI, G., PERK, J., POLONIA, J., POPESCU, B. A., REINER, Ž., RYDÉN, L., SIRENKO, Y., STANTON, A., et al. 2013. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *European Heart Journal,* 34, 2159-2219.

MARCIL, M., BOURDUAS, K., ASCAH, A. & BURELLE, Y. 2006. Exercise training induces respiratory substrate-specific decrease in Ca2+-induced permeability transition pore opening in heart mitochondria. *American Journal of Physiology - Heart and Circulatory Physiology,* 290, H1549-H1557.

MARTIN, D. A., TOWNE, J. E., KRICORIAN, G., KLEKOTKA, P., GUDJONSSON, J. E., KRUEGER, J. G. & RUSSELL, C. B. 2013. The Emerging Role of IL-17 in the Pathogenesis of Psoriasis: Preclinical and Clinical Findings. *J Invest Dermatol,* 133, 17-26.

MARTIN, J. L., MESTRIL, R., HILAL-DANDAN, R., BRUNTON, L. L. & DILLMANN, W. H. 1997. Small Heat Shock Proteins and Protection Against Ischemic Injury in Cardiac Myocytes. *Circulation,* 96, 4343-4348.

MARTINEZ-SALES, V., VILA, V., RICART, J. M., VAYA, A., TODOLI, J., NNNEZ, C., CONTRERAS, T., BALLESTER, C. & REGANON, E. 2015. Increased circulating endothelial cells and microparticles in patients with psoriasis. *Clin Hemorheol Microcirc,* 60, 283-90.

MARTYN-SIMMONS, C. L., RANAWAKA, R. R., CHOWIENCZYK, P., CROOK, M. A., MARBER, M. S., SMITH, C. H. & BARKER, J. N. W. N. 2011. A prospective case-controlled cohort study of endothelial function in patients with moderate to severe psoriasis. *British Journal of Dermatology,* 164, 26-32.

MASON, A. R., MASON, J., CORK, M., DOOLEY, G. & EDWARDS, G. 2009. Topical treatments for chronic plaque psoriasis. *Cochrane Database Syst Rev,* 15.

MATTEI, P. L., COREY, K. C. & KIMBALL, A. B. 2014. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *Journal of the European Academy of Dermatology and Venereology,* 28, 333-337.

MAURY, E. & BRICHARD, S. M. 2010. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Mol Cell Endocrin,* 314, 1-16.

MAZZOTTI, E., PICARDI, A., SAMPOGNA, F., SERA, F., PASQUINI, P., ABENI, D. & THE IDI MULTIPURPOSE PSORIASIS RESEARCH ON VITAL EXPERIENCES STUDY, G. 2003. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *British Journal of Dermatology,* 149, 318-322.

MEAD, G. E., MORLEY, W., CAMPBELL, P., GREIG, C. A., MCMURDO, M. & LAWLOR, D. A. 2008. Exercise for depression. *Cochrane Database Syst Rev,* 8.

MEHLIS, S. L. & GORDON, K. B. 2003. The immunology of psoriasis and biologic immunotherapy. *Journal of the American Academy of Dermatology,* 49, 44-50.

MEHTA, N. N., AZFAR, R. S., SHIN, D. B., NEIMANN, A. L., TROXEL, A. B. & GELFAND, J. M. 2009. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *European Heart Journal*.

MELNIKOVA, I. 2009. Psoriasis market. *Nature Reviews Drug Discovery,* 8, 767-768.

MENDENHALL, L. A., SWANSON, S. C., HABASH, D. L. & COGGAN, A. R. 1994. Ten days of exercise training reduces glucose production and utilization during moderate- intensity

exercise. *American Journal of Physiology - Endocrinology And Metabolism,* 266, E136.

MEYER, N., PAUL, C., FENERON, D., BARDOULAT, I., THIRIET, C., CAMARA, C., SID-MOHAND, D., LE PEN, C. & ORTONNE, J. P. 2010. Psoriasis: an epidemiological evaluation of disease burden in 590 patients. *Journal of the European Academy of Dermatology and Venereology,* 24, 1075-1082.

MILLASSEAU, S. C., STEWART, A. D., PATEL, S. J., REDWOOD, S. R. & CHOWIENCZYK, P. J. 2005. Evaluation of carotid-femoral pulse wave velocity: influence of timing algorithm and heart rate. *Hypertension,* 45, 222-6.

MITRANUN, W., DEEROCHANAWONG, C., TANAKA, H. & SUKSOM, D. 2014. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. *Scandinavian Journal of Medicine & Science in Sports,* 24, e69-e76.

MONTRUCCHIO, G., ALLOATTI, G. & CAMUSSI, G. 2000. Role of Platelet-Activating Factor in Cardiovascular Pathophysiology. *Physiological Reviews,* 80, 1669-1699.

MORA, S., COOK, N., BURING, J. E., RIDKER, P. M. & LEE, I. M. 2007. Physical Activity and Reduced Risk of Cardiovascular Events: Potential Mediating Mechanisms. *Circulation,* 116, 2110-2118.

MORA, S., LEE, I., BURING, J. E. & RIDKER, P. 2006. Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *JAMA,* 295, 1412-1419.

MUSSI, A., BONIFATI, C., CARDUCCI, M., D'AGOSTO, G., PIMPINELLI, F., D'URSO, D., D'AURIA, L., FAZIO, M. & AMEGLIO, F. 1997. Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis. *J Biol Regul Homeost Agents,* 11, 115-8.

MYERS, J. 2003. Exercise and Cardiovascular Health. *Circulation,* 107, e2-e5.

NALDI, L., CONTI, A., CAZZANIGA, S., PATRIZI, A., PAZZAGLIA, M., LANZONI, A., VENEZIANO, L., PELLACANI, G. & THE PSORIASIS EMILIA ROMAGNA STUDY, G. 2014. Diet and physical exercise in psoriasis: a randomized controlled trial. *British Journal of Dermatology,* 170, 634-642.

NALDI, L. & GAMBINI, D. 2007. The clinical spectrum of psoriasis. *Clinics in Dermatology,* 25, 510-518.

NATARAJAN, A., MARSHALL, S. M., KESTEVEN, P. J., MCCOMB, J. M. & RUTTER, M. K. 2011. Impact of biomarkers for endothelial dysfunction and procoagulant state on 10- year cardiovascular risk in Type 2 diabetes1. *Diabetic Medicine,* 28, 1201-1205.

NEIMANN, A. L., SHIN, D. B., WANG, X., MARGOLIS, D. J., TROXEL, A. B. & GELFAND, J. M. 2006. Prevalence of cardiovascular risk factors in patients with psoriasis. *Journal of the American Academy of Dermatology,* 55, 829-835.

NELSON, P. A., ASHCROFT, D. M., BUNDY, C., CHEW-GRAHAM, C. A., CHISHOLM, A., CORDINGLEY, L., DAVIES, L. M., ELVIDGE, J., GRIFFITHS, C. E. M., HAMILTON, M. P., HILTON, R., KANE, K., KEYWORTH, C., LITTLEWOOD, A. J., LOVELL, K., MCATEER, H., NTAIS, D., PARISI, R., PEARCE, C. J., RUTTER, M. K., SYMMONS, D. P. M. & YOUNG, H. S. 2015. The IMPACT Programme in Psoriasis: Phase I – where we are now and future directions. *Dermatological Nursing,* 14, 37-44.

NELSON, M. E., REJESKI, W. J., BLAIR, S. N., DUNCAN, P. W., JUDGE, J. O., KING, A. C., MACERA, C. A. & CASTANEDA-SCEPPA, C. 2007. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation,* 116, 1094.

NELSON, P. A., KEYWORTH, C., CHISHOLM, A., PEARCE, C. J., GRIFFITHS, C. E. M., CORDINGLEY, L., BUNDY, C., THE, I. & MANAGEMENT OF PSORIASIS-

ASSOCIATED

CO-MORBIDITY, T. 2014. 'In someone's clinic but not in mine' – clinicians' views of supporting lifestyle behaviour change in patients with psoriasis: a qualitative interview study. *British Journal of Dermatology,* 171, 1116-1122.

NICHOL, M. B., MARGOLIES, J. E., LIPPA, E., ROWE, M. & QUELL, J. 1996. The application of multiple quality-of-life instruments in individuals with mild-to-moderate psoriasis. *Pharmacoeconomics,* 10, 644-53.

NIJSTEN, T., MEADS, D. M. & MCKENNA, S. P. 2006. Dimensionality of the Dermatology Life Quality Index (DLQI): A Commentary. *Acta Dermato-Venereologica,* 86, 289-290.

O'DONOVAN, C., LITHANDER, F. E., RAFTERY, T., GORMLEY, J., MAHMUD, A. & HUSSEY, J. 2014. Inverse relationship between physical activity and arterial stiffness in adults with hypertension. *J Phys Act Health,* 11, 272-7.

OKITA, K., NISHIJIMA, H., MURAKAMI, T., NAGAI, T., MORITA, N., YONEZAWA, K., IIZUKA, K., KAWAGUCHI, H. & KITABATAKE, A. 2004. Can exercise training with weight loss lower serum C-reactive protein levels? *Arterioscler Thromb Vasc Biol,* 24, 1868-73.

ÖNAL, Z. E., ATASAYAN, V., GÜRBÜZ, T., HEPKAYA, E. & NUHOĞLU, Ç. 2014. Association of glycosylated hemoglobin (HbA1c) levels with Iinsulin resistance in obese children. *African Health Sciences,* 14, 533-538.

PAPP, K. A., KRUEGER, J. G., FELDMAN, S. R., LANGLEY, R. G., THACI, D., TORII, H., TYRING, S., WOLK, R., GARDNER, A. & MEBUS, C. 2016. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. *Journal of the American Academy of Dermatology,* 74, 841-850.

PARISI, R., RUTTER, M. K., LUNT, M., YOUNG, H. S., SYMMONS, D. P., GRIFFITHS, C. E. & ASHCROFT, D. M. 2015. Psoriasis and the Risk of Major Cardiovascular Events: Cohort Study Using the Clinical Practice Research Datalink. *J Invest Dermatol,* 135, 2189-97.

PARISI, R., SYMMONS, D. P. M., GRIFFITHS, C. E. M. & ASHCROFT, D. M. 2013. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *J Invest Dermatol,* 133, 377-385.

PEARCE, D. J., MORRISON, A. E., HIGGINS, K. B., CRANE, M. M., BALKRISHNAN, R., FLEISCHER JR, A. B. & FELDMAN, S. R. 2005. The comorbid state of psoriasis patients in a university dermatology practice. *Journal of Dermatological Treatment,* 16, 319-323.

PENG, H., HAN, S. H., LIU, H. Y., CHANDNI, V., CAI, X. Q. & ZHANG, Y. H. 2013. Relationship of Inflammation and Endothelial Dysfunction with Risks to Cardiovascular Disease among People in Inner Mongolia of China(). *Biomedical and environmental sciences : BES,* 26, 792-800.

PERROTT, S. B., MURRAY, A. H., LOWE, J. & MATHIESON, C. M. 2000. The psychosocial impact of psoriasis: physical severity, quality of life, and stigmatization. *Physiology & Behavior,* 70, 567-571.

PERSEGHIN, G., PRICE, T. B., PETERSEN, K. F., RODEN, M., CLINE, G. W., GEROW, K., ROTHMAN, D. L. & SHULMAN, G. I. 1996. Increased Glucose Transport– Phosphorylation and Muscle Glycogen Synthesis after Exercise Training in Insulin- Resistant Subjects. *New England Journal of Medicine,* 335, 1357-1362.

PETERSEN, A. M. W. & PEDERSEN, B. K. 2005. The anti-inflammatory effect of exercise. *Journal of Applied Physiology,* 98, 1154-1162.

PISCHON, T., HANKINSON, S. E., HOTAMISLIGIL, G. S., RIFAI, N. & RIMM, E. B. 2003. Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. *Obesity research,* 11, 1055-1064.

PLAISANCE, E. P. & GRANDJEAN, P. W. 2006. Physical activity and high-sensitivity C-reactive protein. *Sports medicine (Auckland, N.Z.),* 36, 443-458.

PLOEGER, H. E., TAKKEN, T., DE GREEF, M. H. & TIMMONS, B. W. 2009. The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: a systematic review. *Exerc Immunol Rev,* 15, 6-41.

POIKOLAINEN, K., KARVONEN, J. & PUKKALA, E. 1999. EXcess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. *Archives of Dermatology,* 135, 1490-1493.

POIKOLAINEN, K., REUNALA, T., KARVONEN, J., LAUHARANTA, J. & KÄRKKÄINEN, P. 1990. Alcohol intake: a risk factor for psoriasis in young and middle aged men? *BMJ,* 300. POOLE, R. & BALLANTYNE, A. 2014. Apremilast: First Global Approval. *Drugs,* 74, 825-837. PRINCE, S., ADAMO, K., HAMEL, M., HARDT, J., CONNOR GORBER, S. & TREMBLAY, M. 2008. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *International Journal of Behavioral Nutrition and Physical Activity,* 5, 1-24.

PRODANOVICH, S., KIRSNER, R. S., KRAVETZ, J. D., MA, F., MARTINEZ, L. & FEDERMAN, D. G. 2009. ASsociation of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. *Archives of Dermatology,* 145, 700-703.

PRUETT, S. B. 2003. Stress and the immune system. *Pathophysiology,* 9, 133-153. QUATRESOOZ, P., HERMANNS-LÊ, T., PIÉRARD, G. E., HUMBERT, P., DELVENNE, P. & PIÉRARD-FRANCHIMONT, C. 2012. Ustekinumab in psoriasis immunopathology with emphasis on the Th17-IL23 axis: a primer. *BioMed Research International,* 2012.

RADAK, Z., CHUNG, H. & GOTO, S. 2005. Exercise and hormesis: oxidative stress-related adaptation for successful aging. *Biogerontology,* 6, 71-75.

RAMOS, J. S., DALLECK, L. C., TJONNA, A. E., BEETHAM, K. S. & COOMBES, J. S. 2015. The Impact of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training on Vascular Function: a Systematic Review and Meta-Analysis. *Sports Medicine,* 45, 679-692.

RAPP, S. R., FELDMAN, S. R., EXUM, M. L., FLEISCHER, A. B., JR. & REBOUSSIN, D. M. 1999. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol,* 41, 401-7.

REHMAN, J., LI, J., PARVATHANENI, L., KARLSSON, G., PANCHAL, V. R., TEMM, C. J., MAHENTHIRAN, J. & MARCH, K. L. 2004. Exercise acutely increases circulating endothelial progenitor cells and monocyte-/macrophage-derived angiogenic cells. *Journal of the American College of Cardiology,* 43, 2314-2318.

REICH, K. & GRIFFITHS, C. M. 2008. The relationship between quality of life and skin clearance in moderate-to-severe psoriasis: lessons learnt from clinical trials with infliximab. *Archives of Dermatological Research,* 300, 537-544.

REUBEN, D. B., JUDD-HAMILTON, L., HARRIS, T. B. & SEEMAN, T. E. 2003. The Associations Between Physical Activity and Inflammatory Markers in High-Functioning Older Persons: MacArthur Studies of Successful Aging. *Journal of the American Geriatrics Society,* 51, 1125-1130.

RICHARDS, H. L., FORTUNE, D. G., CHONG, S. L. P., MASON, D. L., SWEENEY, S. K. T., MAIN, C. J. & GRIFFITHS, C. E. M. 2003. Divergent Beliefs About Psoriasis Are Associated with Increased Psychological Distress. *J Investig Dermatol,* 123, 49-56.

RICHARDS, H. L., FORTUNE, D. G., GRIFFITHS, C. E. & MAIN, C. J. 2001. The contribution of perceptions of stigmatisation to disability in patients with psoriasis. *J Psychosom Res,* 50, 11-5.

RICHTER, B., NIESSNER, A., PENKA, M., GRDIĆ, M., STEINER, S., STRASSER, B., ZIEGLER, S.,

ZORN, G., MAURER, G., SIMEON-RUDOLF, V., WOJTA, J. & HUBER, K. 2005.
Endurance training reduces circulating asymmetric dimethylarginine and myeloperoxidase levels in persons at risk of coronary events. *Thrombosis and haemostasis,* 94, 1306-1311.
ROGNMO, Ø., MOHOLDT, T., BAKKEN, H., HOLE, T., MØLSTAD, P., MYHR, N. E., GRIMSMO, J. & WISLØFF, U. 2012. Cardiovascular Risk of High- Versus Moderate-Intensity Aerobic Exercise in Coronary Heart Disease Patients. *Circulation,* 126, 1436-1440.
RUCEVIC, I., PERL, A., BARISIC-DRUSKO, V. & ADAM-PERL, M. 2003. The role of the low energy diet in psoriasis vulgaris treatment. *Coll Antropol,* 1, 41-8.
RZEWNICKI, R., AUWEELE, Y. V. & BOURDEAUDHUIJ, I. D. 2003. Addressing overreporting on the International Physical Activity Questionnaire (IPAQ) telephone survey with a population sample. *Public Health Nutrition,* 6, 299-305 M3 - 10.1079/PHN2002427.
SAETRE, T., ENOKSEN, E., LYBERG, T., STRANDEN, E., JØRGENSEN, J. J., SUNDHAGEN, J. O. & HISDAL, J. 2011. Supervised Exercise Training Reduces Plasma Levels of the Endothelial Inflammatory Markers E-Selectin and ICAM-1 in Patients With Peripheral Arterial Disease. *Angiology,* 62, 301-305.
SALLIS, J. F. 2000. Age-related decline in physical activity: a synthesis of human and animal studies. *Med Sci Sports Exerc,* 32, 1598-600.
SALOMAA, V., RILEY, W., KARK, J. D., NARDO, C. & FOLSOM, A. R. 1995. Non–Insulin-Dependent Diabetes Mellitus and Fasting Glucose and Insulin Concentrations Are Associated With Arterial Stiffness Indexes: The ARIC Study. *Circulation,* 91, 1432- 1443.
SAMARASEKERA, E. J., NEILSON, J. M., WARREN, R. B., PARNHAM, J. & SMITH, C. H. 2013. Incidence of Cardiovascular Disease in Individuals with Psoriasis: A Systematic Review and Meta-Analysis. *J Invest Dermatol,* 133, 2340-2346.
SAMPOGNA, F., CHREN, M. M., MELCHI, C. F., PASQUINI, P., TABOLLI, S., ABENI, D. & THE ITALIAN MULTIPURPOSE PSORIASIS RESEARCH ON VITAL EXPERIENCES STUDY, G.
2006. Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. *British Journal of Dermatology,* 154, 325-331.
SAMPOGNA, F., SERA, F. & ABENI, D. 2004. Measures of Clinical Severity, Quality of Life, and Psychological Distress in Patients with Psoriasis: A Cluster Analysis. *J Investig Dermatol,* 122, 602-607.
SAUDER, D. N. & SAUDER, M. B. 2013. Molecular mechanisms in psoriasis: historical perspective and current pathogenesis. *Expert Review of Dermatology,* 8, 1-3.
SCHAFER, I., HACKER, J., RUSTENBACH, S. J., RADTKE, M., FRANZKE, N. & AUGUSTIN, M. 2010a. Concordance of the Psoriasis Area and Severity Index (PASI) and patient- reported outcomes in psoriasis treatment. *Eur J Dermatol,* 20, 62-7.
SCHAFER, P. H., PARTON, A., GANDHI, A. K., CAPONE, L., ADAMS, M., WU, L., BARTLETT, J. B., LOVELAND, M. A., GILHAR, A., CHEUNG, Y. F., BAILLIE, G. S., HOUSLAY, M. D., MAN, H. W., MULLER, G. W. & STIRLING, D. I. 2010b. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *British Journal of Pharmacology,* 159, 842-855.
SCHINDLER, T. H., HORNIG, B., BUSER, P. T., OLSCHEWSKI, M., MAGOSAKI, N., PFISTERER, M., NITZSCHE, E. U., SOLZBACH, U. & JUST, H. 2003. Prognostic Value of Abnormal Vasoreactivity of Epicardial Coronary Arteries to Sympathetic Stimulation in Patients With Normal Coronary Angiograms. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 23, 495-501.
SCHLAAK, J. F., BUSLAU, M., JOCHUM, W., HERMANN, E., GIRNDT, M., GALLATI, H., BUSCHENFELDE, K.-H. M. Z. & FLEISCHER, B. 1994. T Cells Involved in Psoriasis Vulgaris

Belong to the Th1 Subset. ***J Investig Dermatol,*** **102, 145-149.**

SCHMID-OTT, G., KUNSEBECK, H.-W., JAGER, B., SITTIG, U., HOFSTE, N., OTT, R., MALEWSKI, P. & LAMPRECHT, F. 2005. Significance of the stigmatization experience of psoriasis patients: a 1-year follow-up of the illness and its psychosocial consequences in men and women. ***Acta dermato-venereologica,*** **85, 27-32.**

SCHMITT, J. & WOZEL, G. 2005. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. ***Dermatology,*** **210, 194-9.**

SCHUTZER, K. A. & GRAVES, B. S. 2004. Barriers and motivations to exercise in older adults. ***Preventive Medicine,*** **39, 1056-1061.**

SCOTT, J. 2004. Pathophysiology and biochemistry of cardiovascular disease. ***Current Opinion in Genetics & Development,*** **14, 271-279.**

SEHGAL, P. B. 1990. Interleukin-6: Molecular Pathophysiology. ***J Investig Dermatol,*** **94, 2s-6s.**

SEREFLICAN, B., GOKSUGUR, N., BUGDAYCI, G., POLAT, M. & HAYDAR PARLAK, A. 2016. Serum Visfatin, Adiponectin, and Tumor Necrosis Factor Alpha (TNF-alpha) Levels in Patients with Psoriasis and their Correlation with Disease Severity. ***Acta Dermatovenerol Croat,*** **24, 13-9.**

SETTY, A., CURHAN, G. & CHOI, H. K. 2007. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' health study ii. ***Archives of Internal Medicine,*** **167, 1670-1675.**

SHETH, M. M. P. B. 2009. Clinical spectrum and severity of psoriasis. ***Curr Probl Dermatol,*** **38, 1-20.**

SHIBATA, S., TADA, Y., HAU, C., TATSUTA, A., YAMAMOTO, M., KAMATA, M., KARAKAWA, M., ASANO, Y., MITSUI, H., SUGAYA, M., KADONO, T., SAEKI, H., KANDA, N. & SATO, S. 2011. Adiponectin as an anti-inflammatory factor in the pathogenesis of psoriasis: induction of elevated serum adiponectin levels following therapy. ***British Journal of Dermatology,*** **164, 667-670.**

SHIKIAR, R., WILLIAN, M. K., OKUN, M. M., THOMPSON, C. S. & REVICKI, D. A. 2006. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. ***Health and Quality of Life Outcomes,*** **4, 71-71.**

SHIN, J. Y., LEE, H. R. & LEE, D. C. 2011. Increased arterial stiffness in healthy subjects with high-normal glucose levels and in subjects with pre-diabetes. ***Cardiovasc Diabetol,*** **10, 30.**

SIJIE, T., HAINAI, Y., FENGYING, Y. & JIANXIONG, W. 2012. High intensity interval exercise training in overweight young women. ***J Sports Med Phys Fitness,*** **52, 255-62.**

SIMPSON, K. A. & SINGH, M. A. F. 2008. Effects of Exercise on Adiponectin: A Systematic Review. ***Obesity,*** **16, 241-256.**

SIMPSON, M. J., CHOW, C., MORGENSTERN, H., LUGER, T. A. & ELLIS, C. N. 2015. Comparison of three methods for measuring psoriasis severity in clinical studies (Part 2 of 2): use of quality of life to assess construct validity of the Lattice System Physician's Global Assessment, Psoriasis Area and Severity Index and Static Physician's Global Assessment. ***Journal of the European Academy of Dermatology and Venereology,*** **29, 1415-1420.**

SINGHAL, A., FAROOQI, I. S., COLE, T. J., O'RAHILLY, S., FEWTRELL, M., KATTENHORN, M., LUCAS, A. & DEANFIELD, J. 2002. Influence of Leptin on Arterial Distensibility: A Novel Link Between Obesity and Cardiovascular Disease? ***Circulation,*** **106, 1919- 1924.**

SIVAMANI, R. K., CORREA, G., ONO, Y., BOWEN, M. P., RAYCHAUDHURI, S. P. & MAVERAKIS, E. 2010. BIOLOGICAL THERAPY OF PSORIASIS. ***Indian Journal of***

Dermatology, **55, 161-170.**

SMITH, K. E. & FENSKE, N. A. 2000. Cutaneous manifestations of alcohol abuse. *Journal of the American Academy of Dermatology,* 43, 1-18.

SOLAK TEKIN, N., TEKIN, I. O., BARUT, F. & YILMAZ SIPAHI, E. 2007. Accumulation of Oxidized Low-Density Lipoprotein in Psoriatic Skin and Changes of Plasma Lipid Levels in Psoriatic Patients. *Mediators of inflammation,* 2007.

SPAH, F. 2008. Inflammation in atherosclerosis and psoriasis: common pathogenic mechanisms and the potential for an integrated treatment approach. *Br J Dermatol,* 159 Suppl 2, 10-7.

SPRAGUE, A. H. & KHALIL, R. A. 2009. Inflammatory cytokines in vascular dysfunction and vascular disease. *Biochemical pharmacology,* 78, 539.

SPRINGATE, D. A., PARISI, R., KONTOPANTELIS, E., REEVES, D., GRIFFITHS, C. E. M. & ASHCROFT, D. M. 2017. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. *British Journal of Dermatology,* 176, 650-658.

SPULS, P. I., LECLUSE, L. L. A., POULSEN, M.-L. N. F., BOS, J. D., STERN, R. S. & NIJSTEN, T. 2010. How Good Are Clinical Severity and Outcome Measures for Psoriasis[quest]: Quantitative Evaluation in a Systematic Review. *J Invest Dermatol,* 130, 933-943.

STANGIER, U., EHLERS, A. & GIELER, U. 2003. Measuring adjustment to chronic skin disorders: validation of a self-report measure. *Psychol Assess,* 15, 532-49.

STERN, R. S. 2007. Psoralen and Ultraviolet A Light Therapy for Psoriasis. *New England Journal of Medicine,* 357, 682-690.

STERRY, W., BARKER, J., BOEHNCKE, W. H., BOS, J. D., CHIMENTI, S., CHRISTOPHERS, E., DE LA BRASSINNE, M., FERRANDIZ, C., GRIFFITHS, C., KATSAMBAS, A., KRAGBALLE, K., LYNDE, C., MENTER, A., ORTONNE, J. P., PAPP, K., PRINZ, J., RZANY, B., RONNEVIG, J., SAURAT, J. H., STAHLE, M., STENGEL, F. M., VAN DE KERKHOF, P. & VOORHEES, J. 2004. Biological therapies in the systemic management of psoriasis: International Consensus Conference. *British Journal of Dermatology,* 151, 3-17.

STERRY, W., STROBER, B. E., MENTER, A. & ON BEHALF OF THE INTERNATIONAL PSORIASIS, C. 2007. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. *British Journal of Dermatology,* 157, 649-655.

SUGANAMI, T. & OGAWA, Y. 2010. Adipose tissue macrophages: their role in adipose tissue remodeling. *J Leukoc Biol,* 88, 33-9.

SUGAWARA, J., HAYASHI, K., YOKOI, T. & TANAKA, H. 2008. Age-Associated Elongation of the Ascending Aorta in Adults. *JACC: Cardiovascular Imaging,* 1, 739-748.

SUWAIDI, J. A., HAMASAKI, S., HIGANO, S. T., NISHIMURA, R. A., HOLMES, D. R. & LERMAN, A. 2000. Long-Term Follow-Up of Patients With Mild Coronary Artery Disease and Endothelial Dysfunction. *Circulation,* 101, 948-954.

SZEPIETOWSKI, WA˛SIK, BIELICKA, NOCKOWSKI & NOWOROLSKA 1999. Soluble E-selectin serum levels correlate with disease activity in psoriatic patients. *Clinical and Experimental Dermatology,* 24, 33-36.

TABLAZON, I. D., AL-DABAGH, A., DAVIS, S. & FELDMAN, S. 2013. Risk of Cardiovascular Disorders in Psoriasis Patients. *American Journal of Clinical Dermatology,* 14, 1-7.

TAKAHASHI, H., TSUJI, H., HASHIMOTO, Y., ISHIDA-YAMAMOTO, A. & IIZUKA, H. 2010. Serum cytokines and growth factor levels in Japanese patients with psoriasis. *Clinical and Experimental Dermatology,* 35, 645-649.

TANAKA, N., FUJIOKA, A., TAJIMA, S., ISHIBASHI, A. & HIROSE, S. 2000. Levels of proelafin peptides in the sera of the patients with generalized pustular psoriasis and pustulosis

palmoplantaris. *Acta Derm Venereol* 80, 102-105.
TAYLOR, D. 2014. Physical activity is medicine for older adults. *Postgraduate Medical Journal,* 90, 26-32.
TAYLOR, W. C., BLAIR, S. N., CUMMINGS, S. S., WUN, C. C. & MALINA, R. M. 1999. Childhood and adolescent physical activity patterns and adult physical activity. *Med Sci Sports Exerc,* 31, 118-23.
TEKIN, N. S., TEKIN, I. O., BARUT, F. & SIPAHI, E. Y. 2007. Accumulation of Oxidized Low-Density Lipoprotein in Psoriatic Skin and Changes of Plasma Lipid Levels in Psoriatic Patients. *Mediators of Inflammation,* 2007, 78454.
TENSIOMED. Available: http://www.tensiomed.com/index.php/en/products/arteriograph [Accessed 11.08.2015.
THE REFERENCE VALUES FOR ARTERIAL STIFFNESS, C. 2010. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *European Heart Journal,* 31, 2338-2350. THIJSSEN, D. H., DAWSON, E. A., BLACK, M. A., HOPMAN, M. T., CABLE, N. T. & GREEN, D. J. 2009. Brachial artery blood flow responses to different modalities of lower limb exercise. *Med Sci Sports Exerc,* 41, 1072-9.
THOMPSON, P. D., CROUSE, S. F., GOODPASTER, B., KELLEY, D., MOYNA, N. & PESCATELLO, L. 2001. The acute versus the chronic response to exercise. *Med Sci Sports Exerc,* 33, S438-45; discussion S452-3.
THORAND, B., BAUMERT, J., DÖRING, A., SCHNEIDER, A., CHAMBLESS, L., LÖWEL, H., KOLB, H. & KOENIG, W. 2006. Association of cardiovascular risk factors with markers of endothelial dysfunction in middle-aged men and women. *Thrombosis and Haemostasis,* 95, 134-141.
TJØNNA, A. E., LEE, S. J., ROGNMO, Ø., STØLEN, T. O., BYE, A., HARAM, P. M., LOENNECHEN, J. P., AL-SHARE, Q. Y., SKOGVOLL, E., SLØRDAHL, S. A., KEMI, O. J., NAJJAR, S. M. & WISLØFF, U. 2008. Aerobic Interval Training Versus Continuous Moderate Exercise as a Treatment for the Metabolic Syndrome: A Pilot Study. *Circulation,* 118, 346- 354.
TOBIN, A.-M., VEALE, D. J., FITZGERALD, O., ROGERS, S., COLLINS, P., O'SHEA, D. & KIRBY, B. 2010. Cardiovascular Disease and Risk Factors in Patients with Psoriasis and Psoriatic Arthritis. *The Journal of Rheumatology,* 37, 1386-1394.
TOBIN, A. M., HACKETT, C. B., ROGERS, S., COLLINS, P., RICHARDS, H. L., O'SHEA, D. & KIRBY, B. 2014. Body mass index, waist circumference and HOMA-IR correlate with the Psoriasis Area and Severity Index in patients with psoriasis receiving phototherapy. *British Journal of Dermatology,* 171, 436-438.
TOFT, A. D., JENSEN, L. B., BRUUNSGAARD, H., IBFELT, T., HALKJÆR-KRISTENSEN, J., FEBBRAIO, M. & PEDERSEN, B. K. 2002. Cytokine response to eccentric exercise in young and elderly humans. *American Journal of Physiology - Cell Physiology,* 283, C289-C295.
TORRES, T., ALEXANDRE, J. M., MENDONÇA, D., VASCONCELOS, C., SILVA, B. M. & SELORES, M. 2014. Levels of Physical Activity in Patients with Severe Psoriasis: A Cross- Sectional Questionnaire Study. *American Journal of Clinical Dermatology,* 15, 129- 135.
TRACEY, D., KLARESKOG, L., SASSO, E. H., SALFELD, J. G. & TAK, P. P. 2008. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. *Pharmacology & Therapeutics,* 117, 244-279.
TRELOAR, V. 2010. Integrative dermatology for psoriasis: facts and controversies. *Clinics in Dermatology,* 28, 93-99.
TRITAKIS, V., TZORTZIS, S., IKONOMIDIS, I., DIMA, K., PAVLIDIS, G., TRIVILOU, P., PARASKEVAIDIS, I., KATSIMAGLIS, G., PARISSIS, J. & LEKAKIS, J. 2016. Association
of arterial stiffness with coronary flow reserve in revascularized coronary artery disease

patients. *World Journal of Cardiology,* 8, 231-239.

TROIANO, R. P., BERRIGAN, D., DODD, K. W., MÂSSE, L. C., TILERT, T. & MCDOWELL, M. 2008. Physical activity in the United States measured by accelerometer. *Medicine and science in sports and exercise,* 40, 181-188.

UYSAL, S., YILMAZ, F. M., KARATOPRAK, K., ARTUZ, F. & CUMBUL, N. U. 2014. The levels of serum pentraxin3, CRP, fetuin-A, and insulin in patients with psoriasis. *Eur Rev Med Pharmacol Sci,* 18, 3453-8.

VAN BORTEL, L. M., LAURENT, S., BOUTOUYRIE, P., CHOWIENCZYK, P., CRUICKSHANK, J. K., DE BACKER, T., FILIPOVSKY, J., HUYBRECHTS, S., MATTACE-RASO, F. U., PROTOGEROU, A. D., SCHILLACI, G., SEGERS, P., VERMEERSCH, S. & WEBER, T. 2012. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens,* 30, 445-8.

VAN GAAL, L. F., MERTENS, I. L. & DE BLOCK, C. E. 2006. Mechanisms linking obesity with cardiovascular disease. *Nature,* 444, 875-880.

VASANKARI, T. J., KUJALA, U. M., VASANKARI, T. M. & AHOTUPA, M. 1998. Reduced oxidized LDL levels after a 10-month exercise program. *Med Sci Sports Exerc,* 30, 1496-501.

VERHOEF, M., LOVE, E. J. & ROSE, S. A. 1993. Women's Social Roles and Their Exercise Participation. *Women & Health,* 19, 15-29.

VICTOR, F. C. & GOTTLIEB, A. B. 2002. TNF-alpha and apoptosis: implications for the pathogenesis and treatment of psoriasis. *Journal of drugs in dermatology : JDD,* 1, 264-275.

VION, A. C., RAMKHELAWON, B., LOYER, X., CHIRONI, G., DEVUE, C., LOIRAND, G., TEDGUI, A., LEHOUX, S. & BOULANGER, C. M. 2013. Shear stress regulates endothelial microparticle release. *Circ Res,* 112, 1323-33.

VITA, J. A. 2002. Nitric oxide-dependent vasodilation in human subjects. *In:* ENRIQUE CADENAS, L. P. (ed.) *Methods in Enzymology.* Academic Press.

VLACHOPOULOS, C., AZNAOURIDIS, K. & STEFANADIS, C. 2010. Prediction of Cardiovascular Events and All-Cause Mortality With Arterial StiffnessA Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology,* 55, 1318-1327.

VLACHOPOULOS, C., DIMA, I., AZNAOURIDIS, K., VASILIADOU, C., IOAKEIMIDIS, N., AGGELI, C., TOUTOUZA, M. & STEFANADIS, C. 2005. Acute Systemic Inflammation Increases Arterial Stiffness and Decreases Wave Reflections in Healthy Individuals. *Circulation,* 112, 2193-2200.

WADE, A. G., CRAWFORD, G. M., YOUNG, D., LEMAN, J. & PUMFORD, N. 2016. Severity and management of psoriasis within primary care. *BMC Family Practice,* 17, 145.

WAHL, A. K., GJENGEDAL, E. & HANESTAD, B. R. 2002. The Bodily Suffering of Living with Severe Psoriasis: In-Depth Interviews with 22 Hospitalized Patients with Psoriasis. *Qualitative Health Research,* 12, 250-261.

WAIN, E. M., DARLING, M. I., PLEASS, R. D., BARKER, J. N. W. N. & SMITH, C. H. 2010. Treatment of severe, recalcitrant, chronic plaque psoriasis with fumaric acid esters: a prospective study. *British Journal of Dermatology,* 162, 427-434.

WAKITA, H. & TAKIGAWA, M. 1994. E-selectin and vascular cell adhesion molecule-1 are critical for initial trafficking of helper-inducer/memory T cells in psoriatic plaques. *Archives of Dermatology,* 130, 457.

WANG, F., YE, P., LUO, L., XIAO, W., QI, L., BIAN, S., WU, H., SHENG, L., XIAO, T. & XU, R. 2011. Association of serum lipids with arterial stiffness in a population-based study in Beijing. *European Journal of Clinical Investigation,* 41, 929-936.

WANG, J. S. & LIAO, C. H. 2004. Moderate-intensity exercise suppresses platelet activation and polymorphonuclear leukocyte interaction with surface-adherent platelets under shear flow in men. *Thromb Haemost,* 91, 587-94.

WANNER, M., PROBST-HENSCH, N., KRIEMLER, S., MEIER, F., AUTENRIETH, C. & MARTIN, B. W. 2016. Validation of the long international physical activity questionnaire: Influence of age and language region. *Preventive Medicine Reports,* 3, 250-256.

WARBURTON, D. E. R., NICOL, C. W. & BREDIN, S. S. D. 2006. Health benefits of physical activity: the evidence. *Canadian Medical Association Journal,* 174, 801-809.

WARREN, R. B., KLEYN, C. E. & GULLIVER, W. P. 2011. Cumulative life course impairment in psoriasis: patient perception of disease-related impairment throughout the life course. *British Journal of Dermatology,* 164, 1-14.

WEBER, T., AMMER, M., RAMMER, M., ADJI, A., O'ROURKE, M. F., WASSERTHEURER, S., ROSENKRANZ, S. & EBER, B. 2009. Noninvasive determination of carotid-femoral pulse wave velocity depends critically on assessment of travel distance: a comparison with invasive measurement. *J Hypertens,* 27, 1624-30.

WILSON, N. J., BONIFACE, K., CHAN, J. R., MCKENZIE, B. S., BLUMENSCHEIN, W. M., MATTSON, J. D., BASHAM, B., SMITH, K., CHEN, T., MOREL, F., LECRON, J.-C., KASTELEIN, R. A., CUA, D. J., MCCLANAHAN, T. K., BOWMAN, E. P. & DE WAAL MALEFYT, R. 2007. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol,* 8, 950-957.

WILSON, P. B., BOHJANEN, K. A., INGRAHAM, S. J. & LEON, A. S. 2012. Psoriasis and physical activity: a review. *Journal of the European Academy of Dermatology and Venereology,* 26, 1345-1353.

WISLØFF, U., STØYLEN, A., LOENNECHEN, J. P., BRUVOLD, M., ROGNMO, Ø., HARAM, P. M., TJØNNA, A. E., HELGERUD, J., SLØRDAHL, S. A., LEE, S. J., VIDEM, V., BYE, A., SMITH, G. L., NAJJAR, S. M., ELLINGSEN, Ø. & SKJÆRPE, T. 2007. Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients: A Randomized Study. *Circulation,* 115, 3086-3094.

WOLK, K., MALLBRIS, L., LARSSON, P., ROSENBLAD, A., VINGARD, E. & STAHLE, M. 2009. Excessive body weight and smoking associates with a high risk of onset of plaque psoriasis. *Acta Derm Venereol,* 89, 492-7.

WOMACK, C., NAGELKIRK, P. & COUGHLIN, A. 2003. Exercise-Induced Changes in Coagulation and Fibrinolysis in Healthy Populations and Patients with Cardiovascular Disease. *Sports Medicine,* 33, 795-807.

WOZEL, G. 2008. Psoriasis treatment in difficult locations: scalp, nails, and intertriginous areas. *Clinics in Dermatology,* 26, 448-459.

YANG, A.-L. & CHEN, H.-I. 2003. Chronic exercise reduces adhesion molecules/iNOS expression and partially reverses vascular responsiveness in hypercholesterolemic rabbit aortae. *Atherosclerosis,* 169, 11-17.

YAWALKAR, N., KARLEN, S., HUNGER, R., BRAND, C. U. & BRAATHEN, L. R. 1998. Expression of Interleukin-12 is Increased in Psoriatic Skin. 111, 1053-1057.

YIU, Z. Z. N. & WARREN, R. B. 2016. Novel Oral Therapies for Psoriasis and Psoriatic Arthritis. *American Journal of Clinical Dermatology,* 17, 191-200.

YIU, K. H., YEUNG, C. K., CHAN, H. T., WONG, R. M., TAM, S., LAM, K. F., YAN, G. H., YUE, W. S., CHAN, H. H. & TSE, H. F. 2011. Increased arterial stiffness in patients with psoriasis is associated with active systemic inflammation. *Br J Dermatol,* 164, 514- 20.

YOUN, J.-C., KIM, C., PARK, S., LEE, S.-H., KANG, S.-M., CHOI, D., SON, N. H., SHIN, D.-J. & JANG, Y. 2013. Adiponectin and progression of arterial stiffness in hypertensive patients. *International Journal of Cardiology,* 163, 316-319.

YOUNG, H. S. 2010. Psoriasis as a systemic disease: considerations for the dermatologist when treating psoriasis. *Advances in Psoriasis and Imflammatory Skin Diseases*.

ZIELINSKI, C. E., MELE, F., ASCHENBRENNER, D., JARROSSAY, D., RONCHI, F., GATTORNO,

M., MONTICELLI, S., LANZAVECCHIA, A. & SALLUSTO, F. 2012. Pathogen-induced
human TH17 cells produce IFN-[ggr] or IL-10 and are regulated by IL-1[bgr]. ***Nature,*** **484, 514-518.**

APPENDIX ONE

Participant assessments

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

(August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an *International Physical Activity Prevalence Study* is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

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

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you

did for at least 10 minutes at a time.

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

_____days per week

☐ No vigorous physical activities → *Skip to question 3*

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 have done solely for recreation, sport, exercise, or leisure.

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

This is the end of the questionnaire, thank you for participating.

5. Protocol for IPAQ Short Form

5.1 Continuous Scores

Median values and interquartile ranges can be computed for walking (W), moderate-intensity activities (M), vigorous-intensity activities (V) and a combined total physical activity score. All continuous scores are expressed in MET-minutes/week as defined below.

5.2 MET Values and Formula for Computation of MET-minutes/week

The selected MET values were derived from work undertaken during the IPAQ

Reliability Study undertaken in 2000-2001[1]. Using the Ainsworth et al. Compendium (*Med Sci Sports Med* 2000) an average MET score was derived for each type of activity. For example; all types of walking were included and an average MET value for walking was created. The same procedure was undertaken for moderate-intensity activities and vigorous-intensity activities. The following values continue to be used for the analysis of IPAQ data: Walking = 3.3 METs, Moderate PA = 4.0 METs and Vigorous PA = 8.0 METs. Using these values, four continuous scores are defined:

Walking MET-minutes/week = 3.3 * walking minutes * walking days

Moderate MET-minutes/week = 4.0 * moderate-intensity activity minutes * moderate days

Vigorous MET-minutes/week = 8.0 * vigorous-intensity activity minutes * vigorous-intensity days Total physical activity MET-minutes/week = sum of Walking + Moderate + Vigorous METminutes/week scores.

5.3 Categorical Score

Category 1 Low

This is the lowest level of physical activity. Those individuals who not meet criteria for Categories 2 or 3 are considered to have a ‘low’ physical activity level.

Category 2 Moderate

The pattern of activity to be classified as ‘moderate’ is either of the following criteria:

a) 3 or more days of vigorous-intensity activity of at least 20 minutes per day

OR

b) 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day

OR

c) 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600 MET-minutes/week.

Individuals meeting at least one of the above criteria would be defined as accumulating a minimum level of activity and therefore be classified as ‘moderate’.

Category 3 High

A separate category labelled ‘high’ can be computed to describe higher levels of participation.

The two criteria for classification as ‘high’ are:

a) vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week

OR

b) 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week.

5.4 Sitting Question in IPAQ Short Form

The IPAQ sitting question is an additional indicator variable of time spent in sedentary activity and is not included as part of any summary score of physical activity. Data on sitting should be reported as median values and interquartile ranges. To-date there are few data on sedentary (sitting) behaviours and no well-accepted thresholds for data presented as categorical levels.

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ..... **Date:** .....

Name: ..... **Score:** .....

Address: ..... **Diagnosis:** .....

.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
2.	Over the last week, how embarrassed or self conscious have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from working or studying?	Yes No	❒ ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at work or studying?	A lot A little Not at all	❒ ❒ ❒		
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
10.	Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒

Please check you have answered EVERY question. Thank you.

PSORIASIS AREA AND SEVERITY INDEX (PASI) WORKSHEET

HOSPITAL NO.: .....

PATIENT NAME: .....

DATE OF VISIT: .....

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

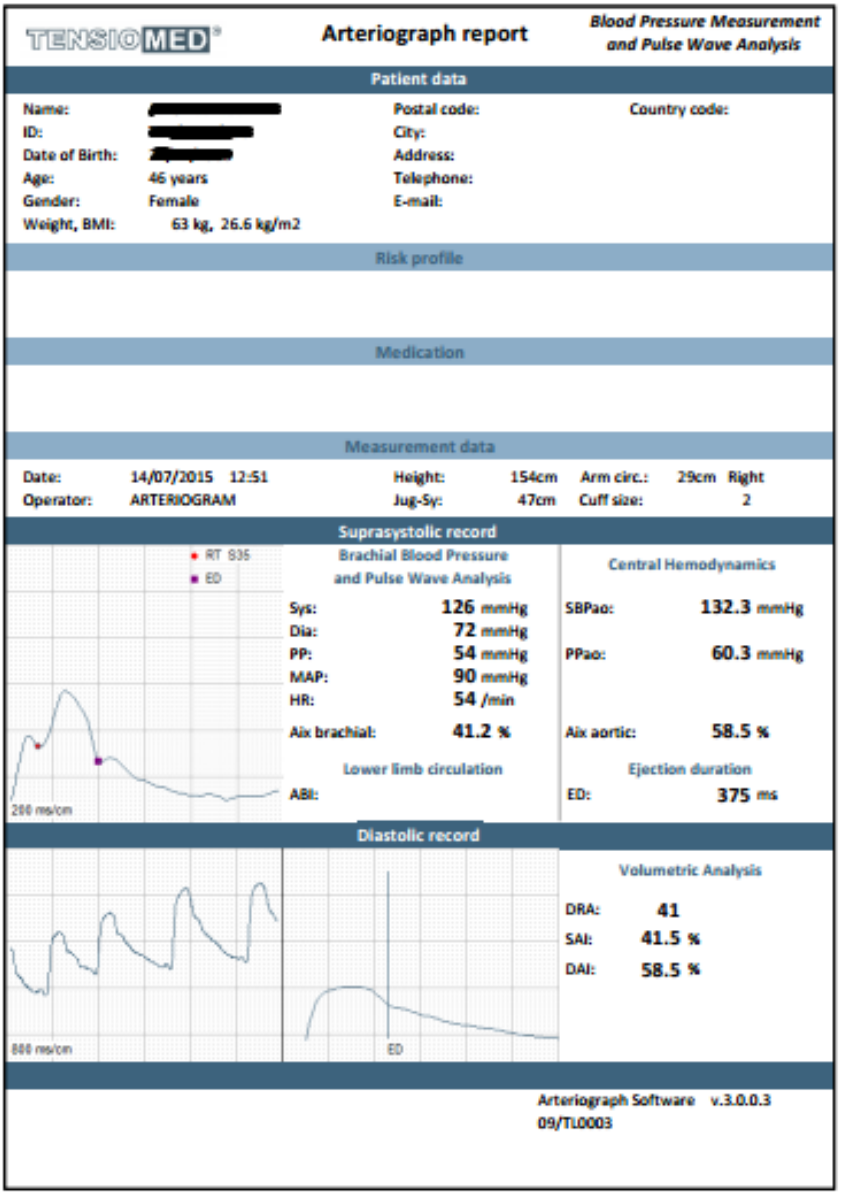
Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		x 0.1	x 0.2	x 0.3	x 0.4
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score = ☐

Example of an arteriograph

Example of an arteriograph



TENSIOMED®

Arteriograph report

Blood Pressure Measurement and Pulse Wave Analysis

Patient data

Name:	[redacted]	Postal code:	Country code:
ID:	[redacted]	City:	
Date of Birth:	[redacted]	Address:	
Age:	46 years	Telephone:	
Gender:	Female	E-mail:	
Weight, BMI:	63 kg, 26.6 kg/m2		

Risk profile

Medication

Measurement data

Date:	14/07/2015 12:51	Height:	154cm	Arm circ.:	29cm Right
Operator:	ARTERIOGRAM	Jug-Sy:	47cm	Cuff size:	2

Suprasystolic record

Brachial Blood Pressure and Pulse Wave Analysis

Sys:	126 mmHg
Dia:	72 mmHg
PP:	54 mmHg
MAP:	90 mmHg
HR:	54 /min
Aix brachial:	41.2 %

Lower limb circulation

ABI:

Central Hemodynamics

SBPao:	132.3 mmHg
PPao:	60.3 mmHg
Aix aortic:	58.5 %

Ejection duration

ED: 375 ms

Diastolic record

Volumetric Analysis

DRA:	41
SAI:	41.5 %
DAI:	58.5 %

Arteriograph Software v.3.0.0.3
09/TL0003

APPENDIX TWO

Training courses attended

UnitCode	Title	Event Date	Event Venue	Hours	Status	StatusChangeDate
FBMHS3010	Final Year: Producing a High Quality PhD/MD Thesis	05/03/2015	2.219 University Place	4	Attended	05/03/2015 15:38
FBMHS2401	Graduate Teaching Assistants/Demonstrator Training	10/11/2014	STDU, Humanities Bridgeford Street	7	Attended	12/11/2014 11:13
TBF22	Data Protection	01/06/2014	Online	0	Attended	02/06/2014 16:25
FMHSS1401	Time Management and Project Planning	21/05/2014	Room 4.38, Simon Building	3	Attended	21/05/2014 15:25
FMHSS2100	Asserting Yourself in a Research Setting	18/12/2013	Room 4.38, Simon Building	4	Attended	18/12/2013 14:14
FMHSS2300	Effective Publications: Taking the sting out of peer review	12/12/2013	Room 4.38, Simon Building	4	Attended	16/12/2013 15:21
FBMHS1202	Research Ethics Application: University & NHS	21/11/2013	Room G306A/B, Jean McFarlane Building	4	Attended	10/02/2014 11:46
FBMHS1403	Making Time for Research	19/11/2013	Room 6.206, University Place	3	Attended	28/11/2013 16:03
FBMHS2303	Systematic Review Training	21/06/2013	Room 4.2, Roscoe Building	7	Attended	25/06/2013 08:24
FMHSS1020	First Year Workshop: Communication Skills	09/05/2013	Lecture Theatre A, University Place	8	Attended	10/05/2013 14:59
FLSCS9310	Career: Business Training for Bioscientists (researchers with an interest in bioscience)	23/04/2013	Core Technology Facility, Grafton Street	4	Attended	23/04/2013 20:07
FMHSS2301	Introduction to Research Governance	08/03/2013	Room 1.009, Roscoe Building	4	Attended	14/03/2013 12:51
FMHSS1203	Research Ethics Application: NHS	07/03/2013	G306A/B, Jean McFarlane Building	4	Attended	14/03/2013 17:01
FMHSS1103	Getting started with your... Literature Review	14/01/2013	Room 5.204, University Place	2	Attended	17/01/2013 10:40
FBMHS1301	Critical analysis of research papers	17/12/2012	Room G306B, Jean McFarlane Building	4	Attended	18/12/2012 09:11
FBMHS1101	An Introduction to Academic Writing	27/11/2012	Room 1.009, Roscoe Building	4	Attended	27/11/2012 15:02
FBMHS1010	First Year: Life as a PhD Student: Getting off to the Best Start	21/09/2012	G306A/B, Jean McFarlane Building	8	Attended	27/09/2012 12:19
MEDNS1001	Health & Safety Module (MEDN)		Online	3	Attended	07/01/2013 10:30