Advancing the case for timely weight loss trials in psoriatic disease by better understanding differences in body composition.

Scientific abstract
Psoriasis is a common chronic inflammatory skin disease affecting 2-3% of the population, with up to 30% developing psoriatic arthritis (PsA). Most treatments directly target the immune system with little focus on effectively tackling excess body weight. Almost 1 in 2 individuals with psoriasis and PsA are now living with obesity. Obesity increases the risk of developing psoriasis, progression to PsA, worse disease activity, poorer treatment response, and greater prevalence of comorbidities including type 2 diabetes, fatty liver, and cardiovascular disease. Consequently, trials of effective weight loss interventions are urgently needed in psoriatic disease to better manage skin and joint disease and metabolic comorbidities. To help guide these interventional studies, we need to better understand the mechanisms by which obesity, particularly the site of fat storage, contributes to psoriatic disease and comorbidities. Our hypothesis is that individuals with psoriasis and PsA store fat differently from people with the same body mass index (BMI) but without psoriatic disease. Small studies suggest more fat is stored around the internal body organs, termed visceral fat, in psoriasis and PsA, and this may be more pro-inflammatory and increase cardiometabolic risk. However, larger studies are needed to confirm this and to identify if specific body fat distributions can predict those at greater risk of psoriasis and PsA and associated heart disease and type 2 diabetes. Those at greatest risk could be prioritised for weight loss interventions.

MRI provides a powerful tool to assess body composition including fat distribution and muscle composition. The UK Biobank, a large prospective population study of 500,000 individuals aged 40-69 years old, including 6,961 individuals with psoriasis and 2,155 with PsA, includes a sub-study of MRI body composition profiles. Using this large dataset, we aim to address the following 1) do people with psoriasis and PsA have more visceral fat and adverse muscle composition than those without psoriatic disease matched on age, sex, and BMI? 2) can body composition profiling predict psoriasis and PsA? 3) can body composition profiling risk stratify people with psoriasis and PsA to identify those at greatest risk of diabetes, heart disease, and all-cause mortality? This will provide better mechanistic understanding of how obesity contributes to psoriatic disease and comorbidities and ultimately help guide inclusion of effective weight loss interventions in disease management guidelines.

Lay abstract
Psoriasis is a common skin condition affecting 2-3 in 100 people. In almost one third, there is also inflammation of joints called psoriatic arthritis (PsA). There are many treatments now available to treat skin and joints, however these all target the immune system. Almost 1 in 2 people with psoriasis and PsA now live with obesity. Obesity increases the chances of developing psoriasis and PsA, results in worse disease, poorer treatment response, and more diabetes and heart disease. We need to find out more about how obesity, in particular fat distribution, contributes to skin and joint disease and related conditions such as diabetes and heart disease. To do this, we will analyse imaging data from the large UK Biobank study. This includes over 500,000 individuals, with several thousand people with psoriasis and PsA. This analysis will ultimately help to develop better weight loss strategies for people with psoriasis and PsA and ensure these are formally included in disease management guidelines. Identifying specific fat distributions and muscle composition patterns using MRI may help identify those at greatest risk of developing psoriasis and PsA, associated conditions including diabetes and heart disease, and those at greatest mortality risk. This could help tailor weight loss interventions to those at greatest risk.

Background

Psoriasis is a common chronic inflammatory skin disease affecting 2-3% of the population[1], of whom up to 30% develop psoriatic arthritis (PsA)[2]. While disease-modifying drugs have significantly improved disease management, these focus on targeting the immune system, and many people have residual skin disease and painful joints. This likely relates to almost 1 in 2 individuals with psoriasis and PsA now living with obesity[3]. Obesity is a major risk factor for developing psoriasis[4], progression to PsA[5], more severe disease, poorer response to treatment[6], and residual pain and fatigue[7]. Obesity is also a key driver of multiple comorbidities in psoriasis and PsA including type 2 diabetes, fatty liver, and cardiovascular disease (CVD)[8]. Despite patients and clinicians increasingly recognising the importance of obesity and weight loss in managing psoriatic disease, current strategies often fail to effectively tackle this. To address patients' priorities to lose weight, trials of effective and sustainable weight loss interventions including GLP-1 agonist therapies in psoriatic disease are urgently needed. To support these, we need to better understand the mechanisms by which obesity contributes to psoriasis and PsA pathogenesis and associated cardiometabolic comorbidities, and if body composition can help identify those most likely to benefit from weight loss therapies.

MRI body composition profiling by our collaborator AMRA provides detailed information about distribution of body fat stores including subcutaneous fat, visceral fat, and ectopic liver fat, and muscle composition including muscle volume and muscle fat infiltration[9]. More fat within visceral stores, termed metabolically unfavourable obesity, is associated with greater risk of diabetes and coronary heart disease (CHD)[10] and may be more pro-inflammatory[11]. Mendelian randomisation studies have suggested this unfavourable adiposity pattern may be the primary cause of psoriasis[12], but sufficient imaging data to support this is lacking.

Pilot data

We have previously shown on genetic analysis that BMI is causally associated with psoriasis[4], and that waist circumference, a surrogate of visceral fat, is associated with greater odds of psoriasis and PsA[13]. In a small pilot study of 28 individuals with PsA, we reported greater visceral and liver fat in PsA compared to BMI matched controls (**figure 1**), with greater propensity to type 2 diabetes and CHD[14]. It is unknown if such a body composition phenotype predicts similar cardiometabolic risk in psoriasis. A small study of 30 individuals with psoriasis and PsA reported greater visceral fat associated with worse disease activity[15]. To date, no-one has assessed if body composition profiling can help predict who will develop psoriasis or PsA, and in those with existing disease, who is at greatest risk of heart disease, diabetes, and death.

Aims

1) Do people with psoriasis and PsA have more visceral fat and adverse muscle composition than age, sex, and BMI-matched controls? 2) can body composition profiling predict psoriasis and PsA? 3) can body composition profiling risk stratify people with psoriasis and PsA to identify those at greatest risk of diabetes, heart disease, and all-cause mortality?

Methods

This study will be conducted using the UK Biobank, a population-based study of over 500,000 participants aged 40-69 years old with a range of conditions including 6,961 individuals with psoriasis and 2,155 with PsA[16]. Existing MRI body composition profiles will be compared between psoriasis, PsA, and a control group of age, sex, and BMI-matched metabolically healthy individuals. A body composition profile is defined as a combination of variables that together described the fat and/or muscle distribution of the group and includes measurements of visceral adipose tissue volume, abdominal subcutaneous adipose tissue volume; liver fat

(%); muscle fat infiltration (%); and thigh fat-free muscle volume. These data will be plotted in six-axis radar charts (body composition plots) using indices and ratios to describe potential skewness in fat distribution patterns as shown in **figure 1.** The propensity for CHD and type 2 diabetes based on body composition profiles will be calculated for psoriasis and PsA according to adaptive k-nearest neighbours algorithm and compared to matched controls[9]. For each participant with psoriasis or PsA, a sex, weight, and height invariant muscle volume z-score will also be calculated. Participants will be partitioned into four muscle composition (MC) groups: (i) normal MC, (ii) low muscle volume, (iii) high muscle fat infiltration, and (iv) adverse MC (low muscle volume z-score and high muscle fat infiltration). Association of MC groups with all-cause mortality in psoriasis and PsA will be investigated using Cox proportional-hazard modelling (normal MC as referent). In a separate analysis, the propensity to develop psoriasis and PsA by body composition will be calculated for the general population according to adaptive k-nearest neighbours algorithm. The UK Biobank study was approved by North West Multicentre Ethics Research Committee.

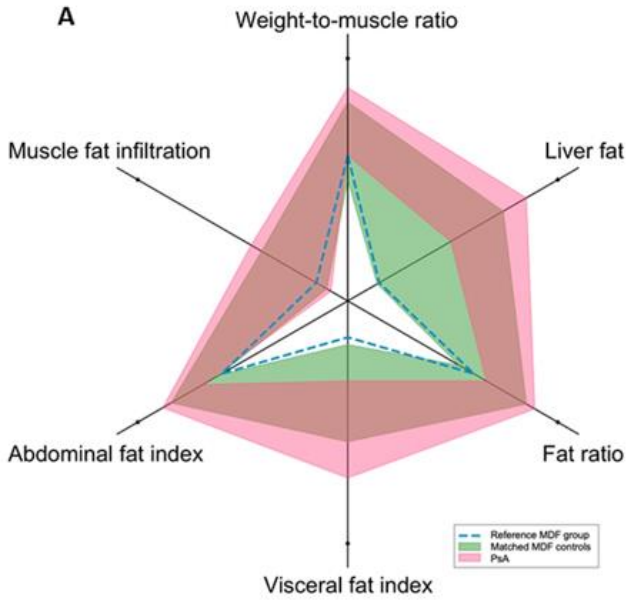

Fig 1. Body composition profile of PsA compared with matched metabolic-disease-free controls[14].

Expected results

We anticipate this large-scale study will confirm individuals with psoriasis and PsA have more visceral fat than people without these conditions but with a similar BMI, and provide new data on adverse muscle composition in psoriatic disease. We expect to identify adverse body composition profiles in psoriasis and PsA that may predict those at greatest risk of diabetes, CHD, and all-cause mortality. Further, we intend to show that individuals with more visceral fat may be at greater risk of developing psoriasis and PsA in the first place.

Significance for psoriatic disease

This study will provide better understanding of the mechanisms by which obesity, particularly visceral fat, contributes to psoriasis and PsA pathogenesis and associated cardiometabolic comorbidities. This will help inform future clinical trials of weight loss therapies in psoriatic disease and inclusion of effective weight management strategies in national treatment guidelines. Identifying those at greater risk of psoriasis and PsA, comorbidities, and all-cause mortality by body composition analysis will also help direct weight loss interventions to those who need them most.

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