RHEUMATOLOGY MUSCULOSKELETAL ULTRASOUND ASSESSMENT OF MINIMAL SYNOVIAL DISEASE IN HANDS, WRISTS AND FEET

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Abstract

Introduction

Ultrasound of joints and tendons is a useful tool in the diagnosis of early inflammatory arthritis. Advances in ultrasound technology in recent years have resulted in better resolution images, facilitating the detection of minimal musculoskeletal structural abnormalities including low grades of synovial hypertrophy, power Doppler signal and joint effusions. However, currently there is no definitive guidance as to what extent these changes may be due to inflammatory arthritis, or how much they are due to the normal ageing process.

Methods

Systematic literature review (SLR): Pubmed, Medline and EMBASE databases were searched: ultrasound, hands, feet, wrists, metacarpophalangeal, metatarsophalangeal, metacarpal, normal, healthy, control, synovial, hypertrophy, Doppler or synovitis. Two independent groups of reviewers assessed the abstracts and subsequent full papers.

Ultrasound of healthy subjects across the age range: Healthy adults (age 18 to 80 years) were recruited in 23 international centres with exclusion criteria: joint pain, hand osteoarthritis and history of inflammatory arthritis. Selected joints and tendons in hands, wrists and feet were scanned and graded according to a recent Outcome Measures in Rheumatology (OMERACT) consensus. Data from a comparison cohort of Rheumatoid Arthritis (RA) patients were taken from the Birmingham Early Arthritis Inception Cohort (BEACON).

Ultrasound findings in patients with clinically suspect arthralgia: The BEACON database was searched for patients with a baseline diagnosis of inflammatory arthralgia or clinically

suspect arthralgia (CSA) who underwent routine ultrasound of selected hand, wrist and foot joints and tendons at time of enrolment, and had 24 month follow up.

Results

SLR: In the 19 full papers included there was considerable heterogeneity in recruitment and definitions of HS, and in the reporting of ultrasound data. This has made it difficult to draw firm conclusions from the evidence gathered in this systematic literature review.

***Ultrasound of healthy subjects across the age range*:** 954 healthy subjects were scanned with a mean age of 44.4 years old. There were significant differences in proportion of grade ≥1 synovial hypertrophy (SH) in metacarpophalangeal joints in older age groups. Prevalence of power Doppler grade ≥1 in all joints was low across the age range. There was variability in prevalence of grade ≥1 SH in wrist and metatarsophalangeal (MTP) joints between recruiting centres, leading to a reliability exercise and creation of new wrist and MTPJ ultrasound atlases. In the digit flexor and extensor carpi ulnaris tendons there was very low prevalence of ultrasound abnormalities with 85% of healthy having grade 0 for all tenosynovial hypertrophy (TSH), power Doppler (TPD) and effusion, with no significant differences across the age range. A comparison cohort of 144 RA patients was compared with a group of age- and sex-matched HS with significant difference in the proportion of TSH and TPD involvement between HS and RA subjects ($p<0.001$).

Ultrasound findings in patients with clinically suspect arthralgia: 43 patients with CSA at baseline diagnosis with 24 month BEACON follow up were included. Positive Rheumatoid factor was associated with development of inflammatory arthritis at 2 years, and ACPA positivity was significantly associated with progression to RA within 2 years ($p<0.05$). There

was significantly more grade ≥1 SH in MCPJ 2 and 3 in those patients that progressed to an inflammatory arthritis by 24 months follow up ($p<0.05$).

Conclusions

This study provides a large amount of ultrasound data on selected joints and tendons for healthy subjects across the age range, and should provide a large control cohort to help further Rheumatology ultrasound research.

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Publications and presentations

PRESENTATIONS/POSTERS:

EULAR Annual Conference Copenhagen June 2022 – poster

ACR Annual Conference Atlanta November 2019 – oral presentation

EULAR Annual Conference Madrid June 2019 – poster

BSR Case Reports Autumn Conference October 2017 - poster

BSR Annual Conference Birmingham April 2017 – poster

BSR Case Reports Autumn Conference, Bath October 2016 – poster

BSR Annual Conference Glasgow April 2016 – poster

BSR Case Reports Autumn Conference, Birmingham October 2015 – oral presentation

BSR Annual Conference Manchester April 2015 – poster

AWARDS:

West Midlands Rheumatology trainee registrars' annual research presentation day (oral presentation) first prize November 2016; second prize November 2017 and February 2019

Owen Wade Prize (oral presentation) West Midlands Physicians' Association (WMPA), Autumn 2015, and collaborator for award in Spring 2016

Midlands Rheumatology Society (MRS) first prize poster presentation, Autumn 2014, second prize poster presentation Spring 2015

Sam Davies Prize for General Practice, final year medical school 2009

PUBLICATIONS:

J Trickey, A Abbas, A Lawley, J Dixey, J Odai; **Hypertrophic cranial pachymeningitis and granulomatosis with polyangiitis**; QJM; Doi: 10.1093/qjmed/hcw012

J Trickey, N Barkham; **Foot and Ankle Insufficiency Fractures in Rheumatoid Arthritis**; Volume 3 Issue 2 - September 2015; http://medcraveonline.com/MOJOR/MOJOR-03-00091.pdf

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Sahbudin I, Singh R, De Pablo P, Rankin E, Rhodes B, Justice E, Derrett-Smith E, Amft N, Narayan N, McGrath C, Baskhar S, Trickey J, Maybury M, Raza K, Filer A. **The value of ultrasound-defined tenosynovitis and synovitis in the prediction of persistent arthritis.** Rheumatology (Oxford). 2022 Apr 12:keac199.doi: 10.1093/rheumatology/keac199. Epub ahead of print. PMID: 35412605.

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List of abbreviations

ACR	American College of Rheumatology
BMI	Body Mass Index
BRC	Biomedical Research Centre
BSR	British Society of Rheumatology
CRP	C Reactive Protein
CSA	Clinically Suspect Arthralgia
CT	Computed Tomography
DAS 28	Disease Activity Score
DF	Digit Flexor
DIP	Distal Interphalangeal
DMARD	Disease Modifying Anti Rheumatic Drug
ECU	Extensor Carpi Ulnaris
EF	Joint Effusion
EMBASE	Excerpta Medica Database
Er	Erosion
ESR	Erythrocyte Sedimentation Rate
EULAR	European Alliance of Associations for Rheumatology
GS	Grey Scale
HDAS	Health Database Advanced Search
HS	Healthy Subject
IA	Inflammatory Arthritis
MCP	Metatcarpophalangeal
MRI	Magnetic Resonance imaging
MRS	Midlands Rheumatology Society
MSUS	Musculoskeletal ultrasound
MTP	Metatarsophalangeal
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OMERACT	Outcome Measures in Rheumatology
Os	Osteophyte
PD	Power Doppler
PIP	Proximal Interphalangeal
PMR	Polymyalgia Rheumatica
PICO	Patients/population, Intervention, Comparison, Outcomes
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analysis Protocol
PROSPERO	International Prospective Register of Systematic Reviews
RA	Rheumatoid Arthritis
SH	Synovial Hypertrophy
TEF	Effusion within tendon sheath
TPD	Tenosynovial Power Doppler
TS	Tenosynovitis
TSH	Tenosynovial Effusion
UIA	Undifferentiated Inflammatory Arthritis
US	Ultrasound
WMPA	West Midlands Physicians Association

1 GENERAL INTRODUCTION

1.1 Inflammatory arthritis

Inflammatory arthritis (IA) is an umbrella term for a range of conditions that feature chronic joint pain, warmth and swelling caused by uncontrolled synovial proliferation. Inflammatory joint pain is often associated with early morning stiffness (lasting 60-120 minutes), pain improving with movement, a diurnal variation with symptoms worse in the mornings, and restricted range of movement of joints. These conditions are often multi-systemic and may affect a wide range of other organs including the skin, lung, heart, eye, kidney, gastro-intestinal system and nervous system. They can be a cause of premature ischaemic heart disease[1] and linked to cancers either from the condition itself or as a consequence of medication.[2] IA may be crystal-mediated, infection-related, autoimmune-mediated in its own right or related to other autoimmune diseases.

Rheumatoid arthritis is the most common chronic inflammatory arthritis, and is the primary condition treated by Rheumatology clinicians with a UK prevalence of around 1%.[3] The most common inflammatory arthritis is gout, mediated by monosodium urate deposits, affecting 2.49% of the UK population.[4] Other common types of inflammatory arthritis include the following: psoriatic arthritis with a prevalence of 0.19% in the general UK population, and 8.6% in patients with confirmed skin psoriasis;[5] axial spondyloarthritis with a prevalence of 0.5%;[6] systemic lupus erythematosus with approximately 0.01% prevalence;[7] and enteropathic arthritis related to inflammatory bowel disease has a prevalence of around 0.7%.[8] Reactive arthritis has an incidence 0.6 to 27 per 100,000 population[9] and is often triggered by gastro-intestinal or genito-urinary infections; it is most common in males in their 20-30s and is usually self-limiting but up to half may go on to have chronic inflammatory arthritis.

1.2 Pathophysiology of Rheumatoid arthritis

The causes of Rheumatoid arthritis are multifactorial and encompass both genetic factors such as HLA-DR1 and HLA-DR4, and environmental factors such as cigarette smoking,[10] diet,[11] and viruses.[12] The gut microbiome is currently a huge area of research for its role in the development of inflammatory arthritis.[13] The presence of specific auto-antibodies such as Rheumatoid Factor (RF),[14] anti-citrullinated protein antibodies (ACPA),[15] and Anti-Acetylated Peptide Antibodies[16] are associated with the development of inflammatory arthritis in asymptomatic subjects, and with more severe disease manifestations in clinically evident RA.

A combination of these factors may trigger the immune system to initiate a cascade of pro-inflammatory cytokines. One target of this response is the synovium of the joint, the membrane of connective tissue lining the joint capsule. This causes proliferation and hyperplasia of the synovium, and an increase in synovial fluid within the joint space. This is termed "synovitis", which if sufficiently severe leads to visible and palpable joint swelling. Synovitis in RA is caused by complex inter-cellular interactions within the synovium involving T cells, B cells, macrophages, and dendritic cells, with activation of pro-inflammatory pathways and cytokines. Over the last twenty years the mediators of this immune response have become targets for biological therapeutic agents such as anti-TNF alpha,[17] anti-B cell therapies,[18] anti-IL 6R[19] and JAK kinase inhibition.[20] The fibroblast is another type of constituent cell of the synovium, producing collagen and extracellular matrix, and is thought to also drive inflammation in arthritis. Recent research has identified fibroblast subsets responsible for more severe inflammatory arthritis which may thus represent future treatment targets.[21]

1.3 Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis with approximately 10% of adults in the UK having a formal diagnosis and symptoms.[22] OA is distinct from RA and has a complex aetiology involving mechanical, genetic and hormonal factors. One of the predominant pathological features of osteoarthritis is the formation of new bone osteophytes at the marginal aspects of the joint.[23] Localised synovial proliferation may be seen in osteoarthritis.[24] However attempts to treat the inflammatory features of osteoarthritis with immunosuppressants traditionally used to treat Rheumatoid arthritis such as Hydroxychloroquine,[25] Methotrexate,[26] or anti-TNF[27] have not been found to be significantly effective. The high prevalence of osteoarthritis, especially in the older population, means that it must be considered as a differential cause of joint pain, swelling and bony changes.

1.4 Presentation of rheumatoid arthritis

Rheumatoid arthritis (RA) most commonly presents between the ages of 40-70 years[28] but can present at a younger age.[29] It is a multisystem autoimmune disease but most classically causes a polyarthritis in a symmetrical distribution affecting metacarpophalangeal, proximal interphalangeal, wrist, elbow, shoulder, knee, ankle and metatarsophalangeal joints. It also commonly affects peri-articular tendons, particularly the digit flexor tendons of the hands and extensor carpi ulnaris tendons of the wrists. Diagnosis of RA is made by history, clinical examination, blood tests for inflammatory markers such as C reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and the presence of the autoantibodies Rheumatoid Factor (RF) and / or Anti-Citrullinated Protein Antibodies (ACPA). Imaging may also support the diagnosis of RA in the form of peri-articular erosion on x-rays, or evidence of synovitis on musculoskeletal ultrasound (MSUS) or magnetic resonance imaging (MRI).

RA may present acutely, insidiously or in a palindromic fashion. It can be associated with a wide range of systemic symptoms such as early morning stiffness, fatigue, fever, weight loss and paraesthesia. RA may have not fully evolved in to a classical presentation fitting EULAR/ACR classification criteria [30] when patients first present to healthcare professionals.

1.5 Classification Criteria for Rheumatoid Arthritis

Rheumatoid arthritis may have been first described by Hippocrates[31] who wrote of a 35 year old patient with rapidly progressive arthritis affecting hands and feet, then going on to involve large joints. The first recognised medical report of RA was in a 1800 dissertation by the French physician Jacob Landre-Beauvais who observed a pattern of arthritis distinct from gout, which was more frequent in female patients from lower socio-economic backgrounds.[32] Major developments in the diagnosis of RA have been made over the last 80 years including the discovery of an antibody in 1940[33] which was later found in patients with RA in 1948 and hence called 'Rheumatoid factor".[34 35]

In 1956, the American Rheumatism Association (ARA) published diagnostic criteria[36] for RA, with the intention of improving accuracy of diagnosis of RA, medical education and communication, and to reduce the variability of RA diagnosis between different research centres. These criteria were revised 30 years later by the ARA in 1987 to distinguish RA from other rheumatological conditions, as over the years there had been advancements in other diagnoses such as HLA-B27 positive spondyloarthropathies[37-39] and calcium pyrophosphate deposition disease.[40] These 1987 ARA revised RA criteria[41] were determined by comparing

characteristics of 262 consecutive patients with established RA against 262 patients with other conditions affecting the joints such as osteoarthritis, psoriatic arthritis and fibromyalgia.

Criterion	Definitions
Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
Arthritis of 3 or more joint areas	At least 3 or more joints areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints
Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP or PIP joint
Symmetric Arthritis	Simultaneous involvement of the same joint area (as defined in point 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry
Rheumatoid nodules	Subcutaneous nodules, over bony prominences or extensor surfaces or in juxta-articular regions observed by a physician
Serum Rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in < 5% of normal control subjects
Radiographic changes	Radiographic changes typical of Rheumatoid arthritis on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

Table 1-1 List format of the 1987 American Rheumatism Association criteria for Rheumatoid Arthritis [41]

Patients need to satisfy at least 4 of the 7 criteria. Criteria 1 to 4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded

Further developments in the diagnosis and treatment of RA were made over the following years, particularly the identification of the mediators driving inflammation in RA such as TNF alpha,[42] IL-1[43] and IL-6.[44] The focus shifted to earlier recognition and immunosuppressive treatment of patients who would go on to develop joint damage. The 1987 ARA classification criteria for RA were found to be limited at identifying patients with very early disease (e.g. radiographic

changes and nodules were infrequent in early RA). Therefore, a group of American and European Rheumatologists developed the 2010 ACR/EULAR RA classification criteria using Delphi consensus and other methods.[30]

A. joint involvement	points	B. serology	points	C. acute phase reactants	points	D. duration of symptoms	points
1 large joint	0	Negative RF *and* negative ACPA	0	Normal CRP *and* normal ESR	0	<6 weeks	0
2-10 large joints	1	Low positive RF *or* low positive ACPA	2	Abnormal CRP *or* abnormal ESR	1	>6 weeks	1
1-3 small joints	2	High positive RF *or* high positive ACPA	3				
4-10 small joints	3						
>10 joints (at least 1 small)	5						

Table 1-2 EULAR/ACR 2020 Rheumatoid Arthritis classification criteria [30]
Patients should have at least 1 joint with definite clinical synovitis (swelling) with the synovitis not better explained by another disease.
Score of 6/10 from sum of points from categories A-D needed for classification of RA

There are a number of differences between the 1987 and 2010 RA classification criteria. The 1987 classification criteria did not include the immunology blood test for anti-citrullinated protein antibody (ACPA). The discovery of ACPA[45] was an important development in the diagnosis of RA. It has a similar sensitivity to RF (67% vs 69% respectively) but is more specific (95% vs 85%) for RA.[46 47] ACPA is important because it predicts RA patients who are more likely to develop radiographic erosions, functional impairment and have more difficult to treat disease.[48-50] Adding ACPA positivity to the 1987 revised criteria for RA was found to

almost double its sensitivity (25% vs 44%) for detecting early RA at more than 6 months since onset of symptoms.[47]

The prevalence of ACPA in the general population is 0.8% when RA patients are excluded (1% including RA patients), and is more common in smokers, older people and those with joint problems[51] compared to 5% of general population having RF positive at low titres.[52-54] ACPA may be present in patients with other Rheumatological conditions such as Sjogrens,[55] SLE[56] and scleroderma [57] but in lower prevalence compared to RA. The prevalence of RA in the UK population is approximately 1%.[58]

The 1987 criteria contain the radiographic presence of erosions, which were seen in up to 60% of patients within the first 12 months of presentation before the 2010 RA classification criteria were published.[59] Presence of bone erosions in RA have been found to be predictive of more severe disease with high morbidity and mortality,[60-62] but the focus should be on earlier diagnosis and treatment of RA before formation or progression of erosions to reduce long term damage.[63] The 2010 RA classification criteria[30] recommends the automatic diagnosis of RA if "classical" RA erosions were present, which were later defined as cortical breaks seen on xrays in three separate sites including proximal interphalangeal joints, metacarpophalangeal joints, wrists and metatarsophalangeal joints.[64]

The1987 RA criteria also includes the clinical presence of Rheumatoid nodules. Although these may occur early in the disease course of RA, they are much more commonly see in Seropositive RA,[65] potentially meaning more patients with seronegative RA are missed or have delayed diagnoses if these criteria are used. The 2010 classification criteria has led to more seronegative

RA patients being included in trials, with research suggesting that seronegative RA is not a milder form of the disease so aggressive early therapy is also needed in these patients.[66]

Treat to target describes the approach of aggressively managing RA, aiming for disease remission[67] with treatment earlier in the disease course being important to reduce disease burden later on.[68] The 2010 classification criteria has helped to capture more of these early patients. Further advances in diagnosis such as ultrasound may support early recognition of RA patients and initiate therapy to lessen future morbidity.

1.6 Early inflammatory arthritis

Early inflammatory arthritis is often thought of as IA within 12 months of onset of symptoms.[69] During this period if patients have an inflammatory arthritis without a precise diagnosis meeting specific classification criteria it may be termed undifferentiated inflammatory arthritis (UIA). Approximately 50% of patients with UIA will spontaneously resolve within weeks to months and a third will go on to develop RA.[70] NICE guidelines recommend Rheumatology assessment and initiation of disease modifying anti rheumatic drugs within 3 months of onset of persistent symptoms.[71]

Inflammatory arthritis may also present with inflammatory type joint pain but with an absence joint swelling on clinical examination. This is termed clinically suspect arthralgia (CSA), and much research is ongoing into which clinical, serological and radiological features may predict patients who go on to have persistent RA or those who spontaneously resolve, and how to induce remission.[72]

1.7 Importance of early initiation of RA treatment

Inflammatory arthritis in its early stages is still not fully understood, and may be self-limiting with full resolution within months[73] or evolve into established and persistent inflammatory arthritis such as RA. Before the introduction of modern conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and biologic DMARDs, patients with RA followed up for 20 years had a mortality from RA of 35%, and severe disability was seen in 20%.[74] Inadequately controlled RA may also be a factor in loss of employment, with up to a third of patients having work disability 5 years after diagnosis.[75] Over the last 15 years there has been an increasing emphasis on treating inflammatory arthritis within the first 3 months of onset of symptoms, because early initiation of DMARDs may result in less severe disease[76] or prevent the progression of arthritis from its early undifferentiated stage where it may still self-resolve on to persistent RA.[77] In those patients who go on to have persistent RA, treatment within 3 months of onset of symptoms is associated with better prognostic, functional, socioeconomic and radiographic outcomes,[78] with evidence that bone erosions causing irreversible joint damage can form early on.[79] Therefore research into helping clinicians diagnose and treat patients at risk of or in the early stages of developing RA is important.

1.8 Clinical measurement of disease activity and monitoring of inflammatory arthritis

The clinical decision to initiate, change, taper or stop DMARDs in patients with inflammatory arthritis is guided and supported by a variety of means of clinical assessment, examination and investigations. These tools also help to determine success or failure of interventions in clinical research. Patient questionnaires are used to assess level of patient reported pain, duration and severity of early morning stiffness, fatigue and global overall health score. Blood tests for inflammatory markers (e.g. CRP and ESR) are helpful if raised and if no signs or suspicion of infection. However, inflammatory markers may be normal in active IA.[80] The primary method

used by clinicians to assess for presence or extent of inflamed joints is by clinical examination of tender and swollen joints which may be part of the DAS 28 (Disease Activity Score) which includes data from an assessment of 28 joints, or other variants including 44 joints and the more comprehensive 66/68 joint count.[81]

1.9 Use of ultrasound in Rheumatology

Clinical examination alone may not always detect active joint inflammation, especially when present at a low level, and imaging may be used in conjunction with patient questionnaires and blood tests to assess disease activity. Imaging has long been used in Rheumatology to aid diagnosis and assess disease damage with plain radiographs detecting erosions and peri-articular osteopenia. Whilst plain radiographs can assess damage to bone and cartilage, newer imaging modalities such as ultrasound and MRI are able to identify inflammation in the synovium, tendons and tendon sheaths, before irreversible structural damage occurs.[82]

Musculoskeletal ultrasound is being increasingly used in routine Rheumatology practice. It is used to identify changes of inflammation and damage in the joints, and is more sensitive than clinical examination and conventional radiography.[83] It may support clinical decision making, meaning that inflammatory arthritis may be diagnosed earlier.[84-87] The adoption of the 2010 RA classification criteria[30] has led to more severe seronegative inflammatory arthritis being diagnosed as RA, so ultrasound may help to diagnose milder or earlier presentations of seronegative RA, and to determine the true extent of disease activity in treated established inflammatory arthritis. Use of ultrasound in Rheumatology may help guide treatment tapering, withdrawal[88] or escalation, although this is controversial. [89]

Magnetic resonance imaging (MRI) is more sensitive than ultrasound because it can detect bone marrow oedema, but the use of ultrasound may be comparable in finding erosions and tenosynovitis in early inflammatory arthritis.[90 91] Some structures are less easy to visualise on MSUS as it cannot penetrate bone, and the transducer needs to make good contact with the surface of skin directly over the structure of interest. Ultrasound has some practical advantages over MRI; it is a point of care tool that can be easily used by trained Rheumatologists to support clinical decision making. It can be portable and used to guide injections in clinic or ward settings. MRI is more expensive, may be more time consuming and there are some limitations upon which patients it may be performed on including: those with certain metal implants / prosthetic heart valves, pacemakers, contrast allergies, claustrophobia or high BMIs. Both MRI and MSUS have advantage over computed tomography (CT) in not involving ionising radiation.

1.9.1 What is ultrasound?

Ultrasound involves the use of transducers containing piezoelectric crystals transmitting sound waves. These sound waves pass through media - when they hit the surface of a different medium, a portion of the sound wave is reflected back to the transducer and displayed as an image, whilst a portion travels further away from the transducer. Tissues such as such as skin, subcutaneous tissue, muscle and fat have different acoustic impedances depending on their densities. The transducer receives these sound waves which are visualised as differing shades of greyscale or echogenicity.[92] Fluid is homogenous and reflects back almost no sound waves so the image seen is completely black and termed “anechoic”. Bone, tendon and air reflect back high proportions of sound waves so the image is seen as bright white or “hyperechoic”. The interface between soft tissue and air reflects back the entire ultrasound beam, so commonly gel is used as a medium between the patient’s skin and the transducer which plugs the air gap and allows sound waves to travel deeper.

There are many potentially confounding factors affecting the quality of the image produced in ultrasonography, which may be user dependent or operator dependent. Resolution of the image is divided into spatial resolution and contrast resolution. Contrast resolution is how easy it is to distinguish between differing degrees of grey scale. Spatial resolution is divided into axial and lateral, referring respectively to how easy it is to distinguish between two objects either on top of each other in the path of the ultrasound beam, or adjacent to each other. Higher frequency ultrasound gives better axial resolution but poorer penetration of deeper tissues. The frequencies of 6-18MHz are typically used in musculoskeletal ultrasound, with the higher range towards 18MHz used to examine more superficial joints such as the metacarpophalangeal joints, and lower frequency towards 6MHz used to examine deeper joints such as shoulders. The frequency needed for ultrasound examination of joints can vary between individual patients, with lower frequencies needed if there is a high thickness of fat layer overlying the joint of interest, or thickened skin such as in scleroderma. The choice of transducer used to scan a joint is determine by the frequency range required and the body part being examined. Linear transducers are typically used to scan joints as they use higher frequencies, and smaller hockey stick probes may be chosen to examine joints in difficult to access areas such as the peroneal tendons posterior to the lateral malleolus.

Gain can be adjusted by the sonographer to increase or decrease the image brightness, making structures easier to see but resolution is affected if gain is increased too much. Time gain compensation can adjust for varying attenuations at different depths of tissues to improve axial resolution. Zoom may be manually adjusted to increase or decrease the size of the ultrasound image, which is necessary when scanning superficial or deep joints. The focal zone may be adjusted on the ultrasound machine to focus the ultrasound beam on the axial level of interest to improve resolution.

1.9.2 Doppler

The Doppler effect describes the change in frequency of a sound wave when it is reflected back from a moving object, and this is important in the application of ultrasound in Rheumatology. Moving erythrocytes in blood vessels reflect ultrasound waves and the Doppler shift is proportional to: the velocity of the flow, the frequency of the ultrasound and the angle between the ultrasound beam and the blood flow (angle of insonation). If blood flow is parallel to the probe (insonation angle is 90 degrees) then no Doppler will be detected, so it is important to vary the angle of the transducer to look for Doppler flow. Colour Doppler displays a colour image of blood flow taken from the mean velocity and direction of the erythrocytes. Power Doppler displays a sum of the detected blood flow irrespective of direction or velocity. Pulse repetition frequency (PRF) is measured in hertz and refers to the number of pulses of sound waves transmitted by the transducer in a set period of time. It may affect Colour Doppler in aliasing artefact, when the Doppler shift of blood vessels is more than half the PRF and reverse flow is seen. PRF may be increased to avoid aliasing artefact but at the cost of decreasing sensitivity to low velocity flow. In musculoskeletal ultrasound, the presence of low velocity flow rather than the direction or velocity of blood flow are important, so Power Doppler is often favoured and PRF kept low.[93] PD settings do not need to vary between patients or joints, so once calibrated the same pre-set can be used for all patients.[94]

Artefacts of Doppler may confound interpretation and are important for the sonographer to be aware of. Pressure applied between the transducer and skin should be kept as light as possible to avoid compressing and missing Doppler flow.[95] Random interference may be seen as background Doppler “noise”, so Doppler gain should be reduced until only a few scattered random artefacts are seen so that true blood flow is not missed. Random noise may also be seen if the patient or transducer moves or if the patient is hot, so these variables must be controlled.

Blooming artefact refers to overspill of Doppler from blood vessels which increases their perceived size on the screen, and it can be managed by reducing the Doppler gain. Mirror artefact occurs when a smooth surface such as the cortex of bone reflects a replica of Doppler flow within the bone creating a false image. Similarly, reverberation artefact is seen when a mirror image of Doppler is reflected from a superficial blood vessel to a deeper area. Therefore it is important to have the Doppler box covering the most superficial section of the joint as well as the area of interest otherwise the reverberation artefact may be misinterpreted as the true Doppler flow.

1.9.3 Musculoskeletal ultrasound pathology

Musculoskeletal ultrasound in Rheumatology practice is used to detect the findings listed in Table 1-3. Synovial hypertrophy (SH) is seen as abnormal hypoechoic signal within the joint capsule and represents inflammatory hyperplasia of the synovial tissue. It is poorly compressible and not displaceable and it may have Power Doppler (PD) signal within it.[96] PD is highly sensitive to flow of blood and can detect neovascularity indicating inflammation within a joint[97] It is the combination of abnormal SH and PD which is regarded as evidence of synovitis on MSUS. Synovial effusion (EF) is seen as abnormal hypoechoic or anechoic signal and is displaceable, but PD is not seen within it. Tenosynovial hypertrophy (TSH), Doppler (TPD) and effusion (TEF) appear similarly to SH, PD and EF on MSUS but relate to findings within the tendon sheath. Tenosynovitis on MSUS is seen as presence of abnormal TSH and TPD.

Ultrasound pathologies	Abbreviation	Explanation
Synovial hypertrophy	SH	Grey scale proliferation of the joint lining
Power Doppler	PD	Indicates neovascularity within an inflamed joint
Joint effusion	EF	Fluid within the joint capsule
Tenosynovial hypertrophy	TSH	Grey scale proliferation of the lining of the tendon sheath
Tenosynovial power Doppler	TPD	Indicates neovascularity within an inflamed tendon sheath
Tenosynovial effusion	TEF	Fluid within the tendon sheath
Osteophyte	Os	A bony prominence, associated with degenerative joint disease
Erosion	Er	Break in bone cortex, caused by inflammation

Table 1-3 List of ultrasound pathologies, with abbreviations and explanations

1.9.4 Significance of Power Doppler in Rheumatoid arthritis

The pathognomonic feature of RA is chronic polyarticular symmetrical joint inflammation, with hypervascularity and hypertrophy of the synovium leading to bone erosion, joint damage, deformity and disability. Ultrasound-detected power Doppler in association with synovial proliferation has been shown to have good correlation with histological evidence of hypervascularity in joints.[98] Ultrasound is more sensitive than clinical examination in detecting synovitis [99] which may explain why patients may still develop bone erosions despite being in clinical remission.[100] Some components of clinical measurement of disease activity such as tender joint counts and global health scores correlate poorly with US-detected synovitis, but there is good correlation of swollen joints and raised inflammatory markers with PD.[101] There is good correlation between ultrasound- and MRI-detected synovitis and tenosynovitis[102] [103] with the benefit of ultrasound being that it is cheaper, quicker, and portable so may be used by Rheumatologists in outpatient clinic settings.

PD can be used to monitor inflammatory joint disease activity, helping clinicians to make decisions on up-titrating, changing, reducing or stopping DMARDs. The dynamic change in

degree of presence of PD has been demonstrated with improvement in MSUS-detected synovitis after anti-TNF therapy [104] and intra-articular steroid injections.[105]

The predictive ability of PD has been demonstrated with presence of PD at baseline diagnosis more strongly correlated than tender or swollen joint count, CRP, ESR or HAQ score with radiographic progression of RA 12 months later.[106] Detection of PD may predict which patients with inflammatory joint symptoms without clinical joint swelling go on to develop persistent inflammatory arthritis.[107] Presence of PD at baseline assessment in MTPJs[87] or in digit flexor tendons in patients negative for RF and ACPA[108] may help to predict patients with early inflammatory arthritis who go on to have persistent inflammatory arthritis 18 months after diagnosis. However, one study found that grade 2 synovial hypertrophy and not PD was associated with early undifferentiated arthritis evolving into persistent rheumatoid arthritis and need for treatment with methotrexate.[109]

1.9.5 Significance of Power Doppler in other forms of inflammatory arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis that may be mono- oligo- or polyarticular and is associated with skin psoriasis. It is diagnosed clinically by CASPAR criteria.[110] The absence of positive autoantibodies such as RF or ACPA, and the fact that inflammatory markers such as CRP may be normal / only minimally elevated, may make it more challenging to diagnose or monitor PsA compared to RA. PsA has distinct features on MSUS compared to RA, with a predominance of extensor peri-tenonitis, proximal interphalangeal joint extensor tendon enthesitis and dactylitis seen more often on ultrasound in early PsA and compared to early RA.[111] [112] Similarly to what has been found in RA, PD at baseline assessment predicts joint damage in PsA.[113]

It is not practical to scan 68 joints that are examined routinely in PsA in addition to multiple entheseal sites. Steps have been made to try to identify composite sites for targeted US in PsA.[114] Ultrasound of patients with clinical oligo-arthritis which is common in psoriatic arthritis or reactive arthritis, has detected more active joints compared to clinical examination, with some being reclassified as having polyarticular disease.[115] Therefore clinical examination in PsA may underestimate the true extent of inflammatory joint disease activity.

Axial spondylitis (axSpa) is characterised by inflammation of the spine and sacro-iliac joints, peripheral joints and entheses. Ultrasound-detected PD at entheses has been found to correlate well with clinical tenderness and swelling at entheseal sites[116] and ultrasound is more sensitive at detecting enthesitis compared to clinical examination.[117] Presence of entheseal PD may help in diagnosis of axSpa in patients with inflammatory back pain not fulfilling ASAS classification criteria for axSpa.[118] Entheseal sites useful to scan include the Achilles tendon, quadriceps and patella tendon and plantar fascia in AxSpa,[119] with the Glasgow Ultrasound Enthesitis Scoring System (GUESS)[117] and Madrid Sonographic Enthesitis Index (MASEI)[120] being commonly used entheseal scanning protocols for enthesitis in both AxSpa and PsA.

In systemic lupus erythematosus (SLE), MSUS findings show a predominance of tenosynovitis and peri-extensor tendon inflammations compared to RA patients.[121] However, US-detected PD has been found in the MCP, PIP, MTP and wrist joints,[122] [123] and in patients with SLE asymptomatic for musculoskeletal problems.[124] Findings of power Doppler at baseline diagnosis has been found to be associated with increased likelihood of musculoskeletal flares[125] and need for methotrexate or hydroxychloroquine at 24 months.[126] Systematic reviews of MSUS findings in patients with SLE have found heterogeneity in data collection, inclusion criteria, scanning methods and joints included, suggesting more work is needed before MSUS in SLE may be used as an outcome measure in clinical trials.[127] [128]

1.9.6 Role of ultrasound in treat to target and withdrawal of treatment

There has been research into whether the addition of ultrasound to guide treat to target in early RA results in better outcomes. The ARCTIC trial found no benefit in up-titration of DMARDs according to US, or US-guided intra-articular steroid injections in tight treat-to target early RA.[129] Also the ARCTIC trial found no difference in MRI-detected inflammation at 2 years after baseline in patients on strict treat-to-target US-guided therapy.[130] Similarly the TASER trial[131] found that treat to target with US in patients with RA of less than one year symptom duration led to more intensive DMARD therapy use but was not associated with better clinical or radiological outcome. However, these studies were under powered to conclude there was no impact on radiographic progression, clinicians were not blinded to the ultrasound results, and there were complicated plans of escalation of treatment, and a low grade of PD counted as positive.[89]

There has also been research into whether US may help guide safe withdrawal of DMARDs, particularly expensive biological DMARDs. In a trial of patients already in clinical remission, patients in US-defined remission had fewer flares, and after 1 year were more likely to be able to step down on DMARD therapy successfully.[132] A higher rate of flare of arthritis after withdrawal of biologics has been noted in patients with evidence of PD synovitis on US but in clinical remission.[133] [134] MSUS may be helpful in decision-making with regards to up-titrating DMARDs, and may allow cost savings especially with biological DMARDs in patients with RA and fibromyalgia.[135]

Further research in to what can be considered "normal" ultrasound findings in the joints that are scanned in Rheumatology would help further research in DMARD treat to target or tapering regimes, allowing a better understanding of what extent of synovial hypertrophy, power Doppler or effusion could be expected to be seen in a normal healthy ageing population.

1.10 Ultrasound grading

Grading of ultrasound parameters is most commonly carried out via a semi-quantitative system. For synovial hypertrophy and joint effusion the findings are classified as normal (grade 0), mild (grade 1), moderate (grade 2), or severe (grade 3).[136] Szkudlarek et al. later described these grades with a further grade 4 where the hypertrophied synovium has expanded over both proximal and distal diaphysis.[90] There is also a quantitative system of grading, but this is more laborious with measurements needing to be taken of all scanned joints. Studies have shown little variability between quantitative and semi quantitative grading systems.[137]

The first steps to reaching an international consensus of definitions for ultrasound defined features of inflammatory arthritis for use in recording outcomes of clinical trials were made in the 2000s.[96] However, some concerns were raised over the reliability of acquisition of standardised images particularly due to the multi-planar aspect of ultrasound, and the intra- and inter-reader variability of the obtained ultrasound images.[138] A more comprehensive consensus of grey scale synovial hypertrophy and power Doppler was published in 2016 by the Outcome Measures in Rheumatology (OMERACT) Ultrasound Working Group.[139] [140] It was the publication of this OMERACT consensus which raised the question of whether it is possible to have widely accepted consensus definitions of grading of pathology that can be applied across the age range, which is the focus of this project.

Comparison of the Szkudlarek[136] and OMERACT0[139] [140] grading protocols shows many similarities but there are a few notable differences (Table 1-4 to 1-6). Synovial hypertrophy (SH) grade 0 and 1 are the same in these 2 grading protocols (Table 1-4). Grade 2 and 3 extend beyond the horizontal joint line in both grading protocols but differ in terms of the shape of the SH; in the OMERACT grades 2 and 3 SH are defined by the concave/convex superficial surface of the synovium (the shape is dominant over extent), whereas Szkudlarek grades 2 and 3 are

defined by whether or not the hypertrophy extends along the diaphysis (the extent is dominant over shape).

Szkudlarek[136]	OMERACT[139 140]
Grade 0 no synovial thickening	Grade 0 (none) No synovial hypertrophy independently of the presence of effusion
Grade 1 minimal synovial thickening (filling the angle between the peri-articular bones without bulging over the line linking tops of the bones)	Grade 1 (minimal) Minimal hypoechoic synovial hypertrophy up to the level of the horizontal line connecting the bone surfaces between the metacarpal head and proximal phalanx
Grade 2 synovial thickening bulging over the line linking tops of the periarticular bones but without extension over the bone diaphysis	Grade 2 (moderate) Moderate hypoechoic SH extending beyond the joint line but with the upper surface concave (curved downwards) or hypertrophy extending beyond the joint line but with the upper surface flat
Grade 3 synovial thickening bulging over the line linking tops of the periarticular bones with extension to at least one of the bone diaphyses	Grade 3 (severe) Severe hypoechoic SH with or without effusion extending beyond the joint line but with the upper surface convex (curved upwards)

Table 1-4 Comparison of synovial hypertrophy gradings
SH, synovial hypertrophy

Comparison of power Doppler grading between Szkudlarek and OMERACT (Table 1-5) shows that grades 0, 2 and 3 are almost identical between the two grading protocols. Grade 1 is further clarified in the OMERACT grading, making it easier to distinguish between grade 1 and 2.

Szkudlarek[136]	OMERACT[139 ,140]
Grade 0 no flow in the synovium	Grade 0 no Doppler signal
Grade 1 single vessel signals	Grade 1 (minimal) up to 3 single Doppler spots OR up to 1 confluent spot and 2 single spots OR up to 2 confluent spots
Grade 2 confluent vessel signals in less than half of the area of the synovium	Grade 2 (moderate) Greater than grade 1 but ≤50% Doppler signals in the total greyscale background
Grade 3 vessel signals in more than half of the area of the synovium	Grade 3 (severe) Greater than grade 2 (>50% of the total greyscale background)

Table 1-5 Comparison of power Doppler gradings

Szkudlarek 2003 [136]	OMERACT 2019 [139 140]
Grade 0 no fluid	Grade 0 no effusion
Grade 1 minimal amount of fluid	Grade 1 minimal amount of joint effusion
Grade 2 moderate amount of fluid (without distension of the joint capsule)	Grade 2 moderate amount of joint effusion (with little distension of the joint capsule)
Grade 3 extensive amount of fluid (with distension of joint capsule)	Grade 3 extensive amount of joint effusion (with high distension of joint capsule)

Table 1-6 Comparison of joint effusion gradings

The joint effusion grading protocols between Szkudlarek and OMERACT (Table 1-6) are almost identical except for grade 2 in the OMERACT grading allows little distension of the joint capsule and high degree is seen in grade 3, as opposed to no joint capsule distension in Szkudlarek's grade 2.

1.10.1 Ultrasound-defined minimal disease

The technology used in ultrasound machines has advanced in recent years resulting in improved resolution of images. This means that low levels of the inflammation associated findings in joints and tendons (listed in Table 1-3) may all be more readily detected. In the general population it is possible some of these ultrasound findings develop as part of the normal ageing process. Although better quality ultrasound images have increased the sensitivity and specificity of detecting ultrasound findings, the ultrasound community has not yet produced substantial healthy control data to distinguish pathological findings related to inflammatory arthritis from normal age-related changes.

The concept of minimal disease in RA was defined by OMERACT consensus in 2005: no tender or swollen joints, low physician and patient global assessments of activity, low health assessment questionnaire (HAQ) score and low inflammatory markers.[141] This minimal disease state was a target to aim for with all RA patients to promote disease remission and prevent long

term joint damage. With ultrasound being more sensitive at detecting joint inflammation than clinical examination alone it has an important role in determining minimal disease activity, and clinical and ultrasound parameters for minimal or low disease activity have been investigated and defined in psoriatic arthritis.[142] In recent years, researchers are increasingly recognising and intervening when patients have symptoms and signs that may represent RA prior to the onset of clinically apparent disease.[143-145] Clinically suspect arthralgia (CSA) is defined by an absence of clinically apparent swelling, but low grade or subclinical disease may be detected on ultrasound.[146] Distinguishing this minimal disease from normal age-related degenerative changes presents a further challenge to ultrasound practitioners. Therefore it is important to define the threshold between normality and pathology throughout the age range.

1.11 Tenosynovitis

Rheumatoid arthritis is most commonly thought of as a condition affecting the joints, but it can also affect tendons, particularly those of the hands and wrists. Tenosynovitis (TS) is a common finding in early DMARD-naïve inflammatory arthritis.[147] Conventional RA disease activity scoring systems focus on joints rather than tendons so clinical examination alone may not detect this pathology.[148] There is better sensitivity in detecting TS in early RA with the use of magnetic resonance imaging (MRI) or musculoskeletal ultrasound (MSUS).[138]

The role and sensitivity of MSUS in detecting subclinical synovial inflammation has been the focus of a vast body of research.[83 149] Additionally, ultrasound has been shown to be highly sensitive in detecting tenosynovial inflammation, with recent studies demonstrating that ultrasound detected hand and wrist tenosynovitis has a role in predicting outcome in early disease and flare in clinical remission.[150 151]

The prevalence of tendon abnormalities in healthy subjects (HS) has been recently studied using MRI.[152] There is limited evidence regarding the prevalence of ultrasound detected tendon abnormalities in HS with most data arising from small case control studies focussed on patients with rheumatic diseases. Many of these studies have not specifically focussed on the prevalence of sonographic tendon abnormalities in HS within the age range of 40 to 70 years when RA may commonly present.[9] Therefore the prevalence of such abnormalities remains unknown in this group.

1.12 Clinically suspect arthralgia

Rheumatoid arthritis (RA) may present with a variety of symptoms and signs before the more characteristic clinical features become apparent fulfilling classification criteria.[153] In the last few years it has been recognised that earlier diagnosis of RA with resulting earlier treatment has more favourable outcomes and may delay progression to RA.[76 77] Therefore, it is important to identify which features predict who will go on to develop RA. Clinically suspect arthralgia (CSA), or inflammatory arthralgia, is a term used when clinicians believe the joint pain and other symptoms experienced by a patient may represent a prelude to developing RA.

In 2017 a European Alliance of Associations for Rheumatology (EULAR) consensus group published guidance on recognising which characteristics of CSA are most important in identifying those at risk of progression on to RA. These parameters are listed In Table 1-7; if ≥3 parameters are present sensitivity is >90%, and if ≥4 parameters present, specificity is >90% for CSA.[143] However, this study represents a consensus of expert opinion, and these characteristics have not been prospectively tested for their ability to differentiate those at risk of developing RA from those that are not.

Joint symptoms of recent onset (duration <1 year)
Symptoms located in MCP joints
Duration of morning stiffness 60 minutes or more
Most severe symptoms present in the early morning
Presence of a first degree relative with RA
Difficulty with making a fist
Positive squeeze test of MCP joints

Table 1-7 European Alliance of Associations for Rheumatology (EULAR) consensus agreed features of clinically suspect arthralgia [143]

MCP, metacarpophalangeal; RA, Rheumatoid Arthritis

There is much research in to which clinical features predict patients who will go on to develop RA or another IA, such as smoking[154] or positive serology for anti-citrullinated protein antibodies (ACPA) and/or Rheumatoid Factor (RF).[155] Imaging has also been used as a predictive tool. In the Leiden cohort of CSA patients; 44% of 93 patients had evidence of inflammation on baseline magnetic resonance imaging (MRI). By follow up four months later, 35% of those with inflammatory MRI findings had developed RA. These signs of inflammation seen on MRI were associated with older age, a positive ACPA, higher body mass index (BMI), higher erythrocyte sedimentation rate (ESR) and a lower tender joint count.[156]

Another study suggested that inflammatory MRI findings at baseline assessment are more important than ACPA positivity in predicting development of RA. Follow up of CSA patients at 1 year showed 43% of those who had developed arthritis were ACPA negative, and 78% had a positive baseline MRI. 60% of those who were ACPA positive but had negative baseline MRI did not develop RA after 1 year. However, of CSA patients who were both ACPA positive and had inflammatory baseline MRI changes, 71% developed RA by 1 year.[157] Therefore, it is possible that combining imaging with autoantibody testing will yield the optimal predictive tool.

Ultrasound is another imaging modality that has predictive value for patients with CSA. In a study of 160 patients with clinically suspect arthralgia, 19% had inflammatory arthritis (IA) by follow up at 12 months. The strongest predictors for development of IA were: positive rheumatoid factor (RF); positive ACPA; early morning stiffness lasting more than 30 minutes; ultrasound detected synovitis (defined as grade 2 or 3 synovial hypertrophy (SH) with or without positive power Doppler (PD)); or positive PD signal at baseline.[158] Similar to MRI, another study suggested that ultrasound detected synovitis may predict development of RA in ACPA negative patients, although that study had some methodological shortcomings including lack of blinding and use of suboptimal equipment.[159]

There may also be some value in the presence of a negative ultrasound scan in predicting those who will not develop RA. A study by van der Ven et al. looked at patients with inflammatory arthralgia in at least two joints for less than one year, with no evidence of joint swelling on clinical examination, and stipulated patients needed at least two of the following features from the Rotterdam Early Arthritis Cohort (REACH) trial:[160] early morning stiffness for more than one hour, inability to form a clenched fist in the morning, pain when shaking hands with someone, paraesthesia in fingers, difficulties wearing rings or shoes, FH of RA, and unexplained fatigue for less than one year. An ultrasound at baseline which was negative for inflammation (defined as grey scale SH < 2 and PD < 1) had an 89% negative predictive value for the development of RA by 12 month follow up.[158]

1.13 Aims and objectives of thesis

Rheumatoid arthritis often presents in middle to old age[161] and a large study that includes older healthy subjects to describe what findings are seen in joints and tendons does not currently exist. The overarching aims of this thesis were to define the normal range of ultrasound findings

in selected joints and tendons in healthy individuals, with a particular focus on the older age range, in order to assess the extent to which ultrasound findings in patients with a new onset of inflammatory arthritis deviate from the normal range.

Hypothesis 1:

Low grades of **synovial hypertrophy** and power Doppler enhancement occur in the joints of healthy individuals in the older age range.

Objective 1: a systematic literature review of ultrasound of metacarpophalangeal, proximal interphalangeal, metatarsophalangeal and wrist joints in healthy subjects.

Objective 2: a large multi-centre ultrasound study of healthy subjects including the older age range to define what is normal on ultrasound.

Hypothesis 2:

Low grades of **tenosynovial hypertrophy** are present in the older healthy population.

Objective: determine the prevalence of ultrasound detected tendon abnormalities in healthy subjects across the age range and compare with a cohort of patients with early RA.

Hypothesis 3:

The presence of clinical and ultrasound features of patients presenting with clinically suspect arthralgia (CSA) may help to predict those patients who will go on to develop clinically evident inflammatory arthritis.

Objective: a retrospective study of CSA patients with 24 month follow up data

2 SYSTEMATIC LITERATURE REVIEW OF ULTRASOUND OF METACARPOPHALANGEAL, PROXIMAL INTERPHALANGEAL, METATARSOPHALANGEAL AND WRIST JOINTS IN HEALTHY SUBJECTS

2.1 Introduction

2.1.1 Rationale

Musculoskeletal ultrasound is increasingly used in routine Rheumatology practice to identify changes of inflammation and damage in the joints, and is more sensitive than clinical examination and conventional radiography[83] meaning that inflammatory arthritis may be diagnosed earlier.[84 85 87 162] Ultrasound may also help to determine the true extent of disease activity in treated established inflammatory arthritis to help guide treatment tapering, withdrawal[88] or escalation, although this is controversial.[89]

With more sophisticated machines being able to detect small changes in synovium, tenosynovium and bone on ultrasound, it is important to have a reference detailing the normal ultrasound appearances of joints, particularly at the older age range of 50-70 years old that Rheumatoid arthritis may typically present.

When initially scoping the literature concerning ultrasound of joints in healthy subjects it was evident that few papers had solely focused on healthy subjects, and there would be insufficient numbers of ultrasound results in healthy subjects for a systematic review. However, a number of studies investigating musculoskeletal ultrasound findings in patients with inflammatory arthritis or other Rheumatic diseases have included a cohort of healthy subjects as controls.

Hypothesis

Low grades of synovial hypertrophy and power Doppler enhancement occur in the joints of healthy individuals in the older age range.

2.1.2 Objectives

The objective of this systematic literature review was to determine the current evidence base for ultrasound of metacarpophalangeal, proximal interphalangeal, metatarsophalangeal and wrist joints in healthy subjects. The PICO for this review is detailed in Table 2-1. The chosen joints are commonly scanned by ultrasound to look for inflammatory arthritis in routine Rheumatology practice.

Population	healthy subjects / healthy controls
Intervention	musculoskeletal ultrasound of joints within the hands, wrists and feet
Comparison	no standard intervention or control to compare against
Outcomes	the grading or measurements of synovial hypertrophy and / or power Doppler in metacarpophalangeal, proximal interphalangeal, wrist and metatarsophalangeal joints

Table 2-1 PICO details for systematic literature review objectives

2.2 Methods

2.2.1 Protocol and registration

No review protocol currently exists but an application for registration on PROSPERO[163] has been made. This literature review has been written using the Preferred Reporting Items for Systematic review and Meta-Analysis Protocol (PRISMA) [164] as the quality assessment tool.

2.2.2 Eligibility criteria

This systematic literature review looked at any study published in the English language after the year 2000 that scanned the small joints of the hands, wrists or feet in adult healthy subjects. The year 2000 was chosen as a cut off to exclude earlier studies using older ultrasound technology with poor resolution images, which would not be comparable to more recent studies. The included studies also needed to include use of a semi–quantitative grading system or a quantitative system to give ultrasound results that could be compared between studies.

2.2.3 Information sources

The initial search was carried out using the National Institute for Healthcare Excellence (NICE) Health Database Advanced Search (HDAS) online tool on 26th February 2019 on EMBASE, Medline and Pubmed databases.

Searches were conducted by a senior Rheumatology trainee (JT) following training provided by the hospital library. Search terms (Table 2-2) for the titles, abstracts and keywords were chosen to capture both papers focussed on healthy subjects, and those in which healthy subjects were used as controls for patients with Rheumatological diseases. Graded or measured ultrasound joint findings in hands, wrists or feet were the desired outcome measure.

2.2.4 Search

Limits placed on EMBASE and Medline results included: English language, date 2000-2019, human age groups 18-64 years or aged 65+ years. The limit function is not available to apply to Pubmed searches on HDAS, but papers published before the year 2000, not in English and

not focussed on adults were manually excluded in the first round of abstract reviews. Additional search terms of "grade" or measure* were used to search the Pubmed database.

ultrasound
AND
hand* OR foot OR feet OR wrist* OR finger*OR toe*OR metacarpophalangeal OR metatarsophalangeal OR metacarpal
AND
normal OR healthy OR control
AND
Rheumatology OR Rheumatoid OR joint*
AND
Synovial OR effusion OR Doppler OR synovitis

Table 2-2 Systemic literature review search terms

The symbol * is used in search terms to include searches with alternative endings such as hand or hands

The search terms in Table 2-2 were formulated and checked using a few key papers[165-167] which were expected to be included in the review, indicating these search terms were broad enough to include important studies. References from selected papers were also checked to search for additional possible useful journal articles.

2.2.5 Repeat search

An additional search was carried out on 9th and 10th July 2019 to include the variation of "ultrasonography" or "sonography" in place of "ultrasound" and also grade or measure*.

2.2.6 Study selection

Search results from the three databases were saved on HDAS and duplicate papers deleted (Figure 2-1). The remaining abstracts were reviewed fully and separately by two independent groups of Rheumatology clinicians acting as reviewers: group 1 (Rheumatology Registrar JT) and group 2 (Rheumatology Associate Specialist VJ and Rheumatology Registrar SP). Six

abstract review criteria were used by both groups to filter through the abstracts (Table 2-3) and were agreed upon to best capture articles including semi-quantitative or quantitative ultrasound data on the metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP) and wrist joints in healthy subjects. These joints were selected because they are routinely investigated by ultrasound in patients with Rheumatoid arthritis.

Number of healthy subjects / controls
Relevant joint (MCPJ, PIPJ, DIPJ, wrist, MTPJ)
Subjects/ controls are healthy
Healthy subjects/controls were scanned with ultrasound
Ultrasound data on healthy controls included
Grading or measurement of SH and/or PD

Table 2-3 Selection criteria data collected to determine inclusion or exclusion of abstracts

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint; SH, synovial hypertrophy; PD, power Doppler

Consensus was reached by the two groups of reviewers on which abstracts fulfilled the initial vetting through discussion and an independent adjudicator (Rheumatology Consultant AF). Abstracts which only existed as a conference abstract with no related full paper article were excluded. Authors were not directly contacted. It was decided that qualifying papers should have examined at least 20 healthy subjects/control, and have ultrasound synovial hypertrophy data as a minimum. Abstracts which did not contain sufficient information to fully exclude them at this stage were allowed through along with the vetted abstracts to the second stage to review the full papers. Exclusion criteria for the full paper articles were agreed upon with the independent adjudicator (Figure 2-1).

2.2.7 Data collection

All abstracts and full papers were reviewed independently by both group 1 and 2, and both groups extracted the data from the final papers (Table 2-4). All headings for data collection were decided prior to extraction. Data were collected by either group 1 or group 2 but were then checked by both groups. Attempt was made to contact the author of one study for clarification of ultrasound results but this was unsuccessful.

Healthy subject details	Recruitment of HS	Scanning details	Ultrasound results
Number	Location of selection	Who scanned	Joints
How were "healthy subjects" defined?	Recruitment time frame	Reliability	SH grade
Mean age	Exclusions	Ultrasound machine/probes and settings	SH measurements
Age range	Number of visits	Scanning environment	PD grades
Number of females	Number of recruitment centres	Scanning protocol	
Mean BMI		Grading or measurement of SH or PD	
Ethnicity		Grading method	
Dominant hand			
Physical activities			
Tender joints			

Table 2-4 Data collected from final full paper articles after full papers vetted

HS, healthy subjects; BMI, body mass index; SH, synovial hypertrophy; PD, power Doppler.

2.2.8 Risk of bias and applicability

The risk of bias in individual studies was assessed using the QUADAS2 tool[168] for patient selection and index test. The reference standard and the flow and timing criteria of the QUADAS2 tool did not apply so were not used.

2.2.9 Synthesis of results

The studies which had data for proportion of joints with grade ≥ 1 for synovial hypertrophy or power Doppler seen on ultrasound, for individual metacarpophalangeal, proximal interphalangeal, metatarsophalangeal or wrist joints, were examined using Stata V13 software. Forest plots were produced using a metaprop command[169] to display confidence intervals.

2.3 Results

2.3.1 Study selection

A total of 297 abstracts were reviewed in the first round, leading to 69 full articles which were vetted in the second round by both groups. At this stage one paper was substituted as it referenced an earlier published article which contained the ultrasound data.[170 171] There were 19 papers with data on healthy subjects included in the final review (Figure 2-1), of which only seven had healthy subjects as the primary focus.

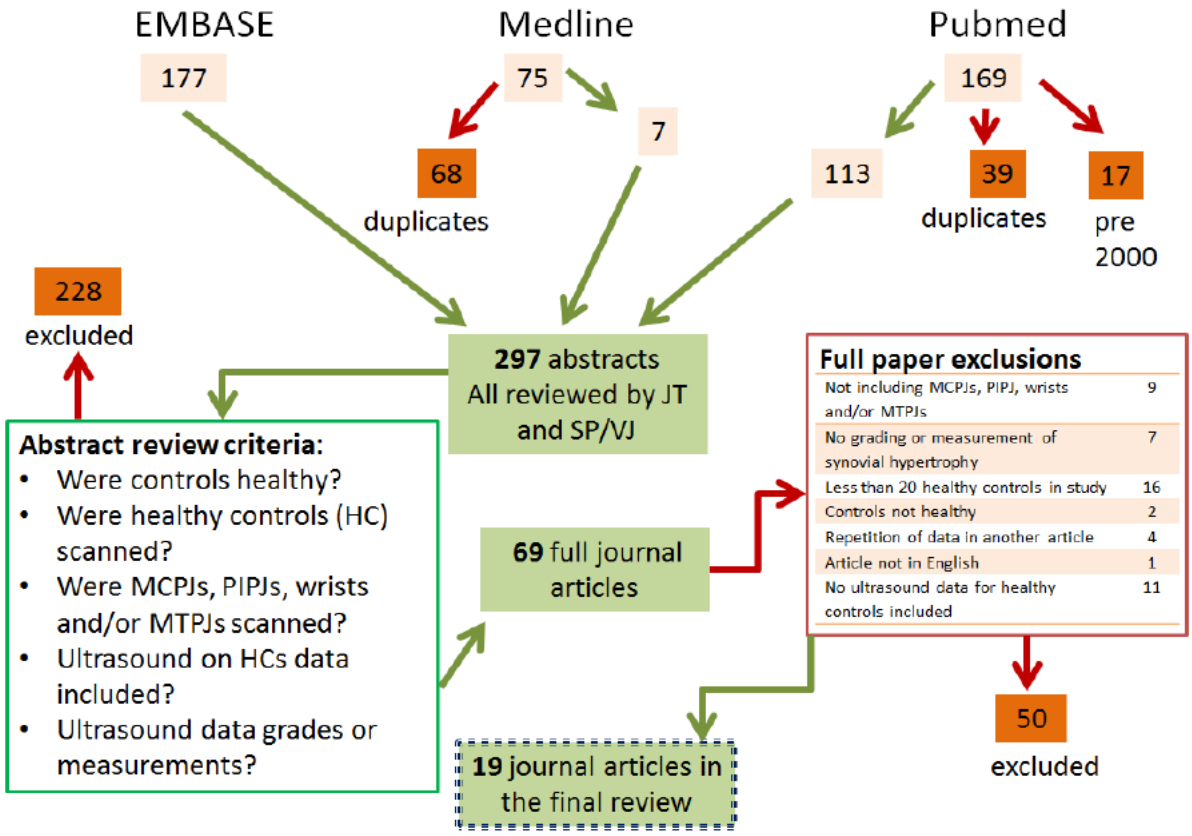

Figure 2-1 PRISMA flow diagram of databases search results, abstract review criteria and exclusions and full paper exclusions

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint

2.3.2 Additional search

An additional search was carried out in July 2019. No further papers were found that could be included in this systematic review. The reasons for exclusions are listed in Table 2-5.

Database	Results	Reason excluded	Number
EMBASE	103	Duplicates	85
		Conference abstracts	11
		Joints not scanned	1
		No healthy controls	3
		Less than 20 healthy controls	2
		No synovial hypertrophy scanned	1
Medline	47	Duplicates	46
		No healthy controls	1
Pubmed	2	Duplicates	2

Table 2-5 Additional search results and reasons for exclusions

2.3.3 Healthy subject recruitment

Over half of the studies (11/19) recruited healthy subjects from health care staff (see Table 2-6), with other recruitment areas including students, friends/relatives of staff or patients, and the general public. One study conducted a targeted recruitment of 20 females and 6 males in each age decade. The definition of healthy varied between studies, with one group using patients with sciatica.

Studies	health care staff	relatives / friends of staff	students	healthy relatives of patients	general public	number of recruitment centres
Micu et al. 2018[172]	y			y		1
Machado et al. 2017[173]					y*	1
Manik et al. 2016[174]	y	y				1
Piga et al. 2016[175]	y					1
Stewart et al. 2016[176]	y					1
Amitai et al. 2015[177]						1
Fodor et al. 2015[178]	y					1
Hiraga et al. 2015[179]	y					1
Padovano et al. 2015[165]	y		y	y	y	1
Cabrera-Villalba et al. 2014[180]	y					1
Sant'Ana Petterle et al. 2013[181]				y		4
Witt et al. 2013[182]						1
Keen et al. 2011[183]						1
Millot et al. 2011[167]	y				sciatica patients	1
Riente et al. 2009[184]						4
Hameed et al. 2008[185]						1
Rosenburg et al. 2008[171]	y		y			1
Ellegaard et al. 2007[186]						1
Schmidt et al. 2004[166]	y	y	y			1

Table 2-6 Healthy subject recruitment

y = studies recruited healthy subjects from these populations
*20 female and 6 male in each age decade scanned

2.3.4 Definition of healthy subjects

The reporting of how each study in this systematic review defined their healthy subjects varied considerably (see Table 2-7). Some studies simply stated that subjects were healthy. The most common exclusion was the presence of osteoarthritis or inflammatory arthritis in 84.2% (16/19) of studies, although there was variation in how this was defined. Subjects with joint pain were excluded in 68.4% (13/19) of studies, and 47.4% (9/19) of studies excluded those with swollen joints or with a recent history of joint trauma. Relatively few studies performed blood test investigations on healthy subjects to ensure that inflammatory markers and Rheumatoid arthritis serology were normal (2/19 and 1/19 respectively).

Studies	joint pain	swollen joints	IA/OA	joint trauma	joint surgery	positive RF / ACPA	raised CRP / ESR	pregnancy	NSAID / cortico-steroid use	FH of IA	possible reactive arthritis
Micu et al. 2018[172]		x	x	x				x	x	x	
Machado et al. 2017[173]	x	x	x	x	x			x			
Manik et al. 2016[174]	x	x	x	x	x	x	x				
Piga et al. 2016[175]											
Stewart et al. 2016[176]	x	x	x		x						
Amitai et al. 2015[177]	x	x	x								
Fodor et al. 2015[178]	x	x	x	x	x						
Hiraga et al. 2015[179]	x		x	x							
Padovano et al. 2015[165]	x	x	x	x							x
Cabrera-Villalba et al. 2014[180]											
Sant'Ana Petterle et al. 2013[181]		x	x	x	x						
Witt et al. 2013[182]	x		x								
Keen et al. 2011[183]	x		x		x			x	x		
Millot et al. 2011[167]	x		x		x						
Riente et al. 2009[184]											

Studies	joint pain	swollen joints	IA/OA	joint trauma	joint surgery	positive RF / ACPA	raised CRP / ESR	pregnancy	NSAID / cortico-steroid use	FH of IA	possible reactive arthritis
Hameed et al. 2008[185]	x	x	x								
Rosenburg et al. 2008[171]	x		x	x							
Ellegaard et al. 2007[186]	x		x	x			x				
Schmidt et al. 2004[166]			x		x						

Table 2-7 Exclusion criteria for healthy subjects

x = if these criteria were present participants were deemed not healthy and excluded from that study

IA, inflammatory arthritis; OA, osteoarthritis; RF, Rheumatoid factor; ACPA, anti- citrullinated protein antibody; CRP, C reactive protein; ESR, estimated sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; FH, family history

2.3.5 Risk of bias and applicability

The recruitment of healthy subjects across the different studies and use of ultrasound on these healthy subjects was evaluated using QUADAS2[168] (see Table 2-8). The risk of bias was deemed as: low, high, or "unclear" if there was not enough information in the article to determine the risk of bias. Overall there was low risk that the subjects in the studies were not healthy, with all studies avoiding inappropriate exclusions. However, studies reported different definitions of healthy (see Table 2-7), and one study recruited healthy subjects with sciatica[167] which although is not a direct sequela of inflammatory arthritis, sciatica can be linked to underlying generalised osteoarthritis.

In most studies, exactly how the healthy subjects were selected from different populations was not specified, with only one study consecutively recruiting healthy subjects.[177] This has led to all but one study having high or unclear risk of bias of recruitment of HS according to the QUADAS tool in Table 2-8. Over half of the studies recruited healthy subjects from health care professionals presumably due to ease of access of these HS (Table 2-7). This could potentially introduce bias as health care professionals are not representative of the healthy general public: doing less manual labour, and are by definition are in paid employment so do not represent retired or unemployed members of society. Health care professionals may have different smoking prevalence compared to the general public. In many studies healthy subjects were recruited as healthy controls for cases of patients with Rheumatic conditions which may introduce bias because the healthy subjects may have characteristics of the population with the disease being examined instead of being representative of the healthy population.

	Healthy subject selection		Index test – ultrasound	
Study	**Risk of bias**	**Concern that included patients do not match the review question**	**Could conduct or interpretation of the index test have introduced bias?**	**Concern the index test, its conduct or interpretation differ from review question?**
Machado *et al. 2017*[173]	high	low	low	low
Manik *et al. 2016*[187]	high	low	unclear	low
Fodor *et al. 2015*[178]	unclear	low	unclear	low
Keen *et al. 2011*[183]	high	low	unclear	low
Hameed *et al. 2008*[185]	high	low	unclear	low
Schmidt *et al. 2004*[166]	unclear	low	unclear	low
Micu *et al. 2018*[172]	high	low	unclear	low
Stewart *et al. 2016* [176]	high	low	low	unclear
Piga *et al. 2016*[175]	high	low	low	low
Padovano *et al. 2015*[165]	unclear	low	low	low
Amitai *et al. 2015*[177]	low	low	unclear	low
Hiraga *et al. 2015* [179]	unclear	low	unclear	unclear
Cabrera-Villalba *et al. 2014*[180]	high	low	unclear	low
Witt *et al. 2013*[182]	high	low	unclear	low
Sant'Ana Petterle *et al. 2013*[181]	high	low	low	unclear
Millot *et al. 2011*[167]	high	high	unclear	unclear
Rosenburg *et al. 2008*[171]	unclear	low	unclear	low
Riente *et al. 2009*[184]	high	low	unclear	low
Ellegaard *et al. 2007* [186]	unclear	low	unclear	low

Table 2-8 QUADAS 2 assessment of risk of bias and applicability of patient selection and index test

With regards to the index test (the ultrasound assessment of selected joints) only five studies stated that the ultrasound machine operator was blinded to any physical information from the clinical assessment of the healthy subjects, which may have introduced bias (Table 2-8). Many of the studies used the one of three semi-quantitative grading systems[96 136 188] to grade joint findings in healthy subjects, meaning there would be low risk of bias in interpreting these results. Some studies used their own grading system or it was not documented (Table 2-8).

2.3.6 Heathy subject demographics

The mean age in the majority of studies was over 40 years (14/19) (see Table 2-9). Most healthy subjects were female, with similar proportions in most studies to the prevalence of RA in females. There was no documentation of mean BMI in 13/19 studies. Six of the centres were based outside Europe, but only four of the centres specified the ethnicities of healthy subjects, which were predominantly Caucasian.

Study	Title and summary	Mean age of HS ± SD (range), years	HS females n (%)	HS mean BMI ± SD	Country; Ethnicity of HS
Machado *et al.*[173]	"Sonographic cut off values for detection of abnormalities in small, medium and large joint: comparative study between patients with RA and healthy volunteers" Cross-sectional study of 60 RA patients and 78 HS, with quantitative synovial recess measurements and semiquantitative grading of SH and PD to determine cut off for detecting RA.	44.8 ± 14.6 (18-80)	100 (76.9%)	25.9 ± 4.5	Brazil; Caucasian 81 (62.3%)
Hussein Manik *et al.*[187]	"Ultrasound assessment of synovial thickness of some of the metacarpophalangeal joints of hand in RA patients and the normal population" Cross-sectional study of 30 RA patients and 30 HS with quantitative thickness of bilateral MCPJ 2-4 measured	46.63 ± 14.3 (ND)	21 (70%)	ND	Malaysia
Fodor *et al.*[178]	"Ultrasonography of the metacarpophalangeal joints in healthy subjects using a 18 MHz transducer" 50 HS groups into age deciles (30-39, 40-49, 50-59 years) to determine ultrasound grades of SH and PD in bilateral MCPJ 1-5. HS scanned by one experienced pair and one inexperienced pair of sonographers	41.7 ± ND (30-58)	37 (74%)	24.43, 26.97, 29.93*	Romania
Keen *et al.*[183]	"An ultrasonographic study of metatarsophalangeal joint pain: synovitis, structural pathology and their relationship to symptoms and function" 33 subjects with first MTPJ pain and 20 asymptomatic HS had bilateral MTPJ 1-5 scanned for grading of SH, PD and Os	60.3 ± 11.6 (27-80)	13 (65%)	ND	Australia and UK
Hameed *et al*[185]	"The relation between composite ultrasound measures and the DAS28 score, its component and acute phase markers in adult RA" 50 RA patients and 25 HS scanned with grading of SH and PD in bilateral MCPJ 1-5 and PIPJ 1-5	45 ± ND (24-62)	17 (68%)	ND	UK

Study	Title and summary	Mean age of HS ± SD (range), years	HS females n (%)	HS mean BMI ± SD	Country; Ethnicity of HS
Schmidt *et al.*[166]	"Standard ultrasound reference values for musculoskeletal ultrasonography" 102 HS aged 20-60 years scanned with ultrasound measurements of many musculoskeletal structures including hypoechoic rims and diameters of bursa and cartilage in joints including bilateral MCPJ 2, PIPJ 2, MTPJ 1 and 2	38.4 ± ND (20-60)	54 (52.3%)	23.6	Germany; Caucasian 102 (100%)
Micu *et al.*[172]	"Pregnant versus non-pregnant healthy subjects – a prospective longitudinal musculoskeletal ultrasound study concerning the spectrum of normality" Cross-sectional study of 75 healthy pregnant women (scanned in each trimester and twice post-partum) and 75 age and sex matched HS (scanned once) with grading of bilateral MCPJ 1-5, PIPJ 1-5, MTPJ 1-5 and wrists.	31.88 ± 8.11 (18-45)	75 (100%)	ND	Romania
Stewart *et al.* [176]	"Ultrasound features of the first metatarsophalangeal joint in gout asymptomatic hyperuricaemia: comparison with normouricemic individuals" 23 patients with gout, 29 patients with hyperuricaemia and 34 age and sex matched HS with normouricaemia had grading of SH and PD in bilateral MTPJ1	58 ± 14 (ND)	0 (0%)	25 ±2.9	New Zealand; Caucasian 30 (88%) Maori 1 (3%) Asian 3 (9%)
Piga *et al.* [175]	"Predictors of musculoskeletal flare and Jaccoud's arthropathy in patients with SLE: A 5 year prospective study" 80 patients with SLE and 48 HS had grading of SH and PD in bilateral MCPJ 2 and 3 and wrists at baseline and year 5. Patients with SLE additionally reviewed 6 monthly and had US if flaring.	49.6 ± 11.6 (ND)	42 (88%)	ND	Italy
Padovano *et al.*[165]	"Prevalence of ultrasound synovial inflammatory findings in HS" 182 HS had grading of SH and PD in bilateral MCPJ 1-5, PIPJ 1-5, MTPJ 1-5 and wrist joints	35.5 ±12.8 (18-74)	146 (71%)	ND	France; Caucasian 173 (84%) Afro-Caribbean 30 (14%) Asian 4 (2%)
Amitai *et al.* [177]	"Comparison of photo optical imaging with musculoskeletal ultrasound and clinical examination in the assessment of inflammatory activity in proximal interphalangeal joints in RA and OA" 38 patients with RA, 21 patients with OA and 28 HS had grading of SH and PD in bilateral PIPJ 2-5 and results compared with photo optimal imaging	28 ± 7 (23-51)	21 (75%)	ND	Germany

Study	Title and summary	Mean age of HS ± SD (range), years	HS females n (%)	HS mean BMI ± SD	Country; Ethnicity of HS
Hiraga *et al.*[179]	"Sonographic measurements of low-echoic synovial area in the dorsal aspect of the metatarsophalangeal joints in HS" 100 HS had measurements of bilateral MTPJ 1-5 SH	41 ± 10.2 (ND)	73 (73%)	21.6	Japan
Cabrera-Villalba *et al.*[180]	"Is there subclinical synovitis in patients with palindromic rheumatism in the inter-critical period? A clinical and ultrasonographic study according to ACPA status" 54 patients with palindromic rheumatism and 30 HS had grading of SH and PD in bilateral MCPJ 1-5, PIPJ 1-5 and wrists	ND[#]	19 (63%)	ND	Spain
Witt *et al.*[182]	"Relevance of grade 1 grey-scale ultrasound findings in the wrists and small joints to the assessment of subclinical synovitis in RA" 100 patients with early or establishes RA and 30 HS had grading of SH and PD in bilateral MCPJ 1-5, PIPJ 1-5, MTPJ 1-5 and wrists	52 ± 17 (ND)	22 (73.3%)	ND	Germany
Sant'Ana Petterle *et al.*[181]	"Usefulness of ultrasound to show subclinical joint abnormalities in asymptomatic feet of RA patients compared to healthy controls" 50 HS and 50 RA patients with asymptomatic feet had grading of SH and PD in bilateral MTPJ 1-5	49.2 ± 11.4 (18-65)	43 (86%)	27.55 ± 4.26	Brazil
Millot *et al.*[167]	"Musculoskeletal ultrasonography in HS and ultrasound criteria for early arthritis" 127 patients with early arthritis matched with 127 HS had grading of SH and PD in MCPJ 2-5 and MTPJ 5	50 ± 12.7 (ND)	99 (78%)	ND	France
Rosenburg *et al.*[171]	"High frequency ultrasonographic effusion in interphalangeal joints of HS: a descriptive study" 46 adult HS < 40 years old had grading of SH in bilateral PIPJ 2-5 but main focus was measurement of effusion	25 ± 5.4 (18-39)	33 (71.7%)	ND	France
Riente *et al.*[184]	"Ultrasound imaging for the rheumatologist XXII. Sonographic evaluation of hand joint involvement in primary Sjogren's syndrome" 48 patients with primary Sjogrens syndrome and 40 HS had grading of SH and PD in bilateral MCPJ 1-5 and PIPJ 2-5	52 ± ND (28-75)	37 (92.5%)	ND	Italy
Ellegaard *et al.*[186]	"Ultrasound in finger joints: findings in normal subjects and pitfalls in the diagnosis of synovial disease" 24 HS had grading of SH in dominant hand MCPJ 1-5 and PIPJ 1-5 using two different scoring systems	44 ± ND (30-54)	12 (50%)	ND	Denmark

Table 2-9 Focus of study and demographics of healthy subjects in each study

ND, not documented; SD, standard deviation; HS, healthy subjects, RA, Rheumatoid Arthritis, SLE, systemic lupus erythematosus; OA, osteoarthritis; P, palindromic rheumatism; MTPJ, metatarsophalangeal joint. SH, synovial hypertrophy; PD, Power Doppler; Os, osteophytes; ACPA, anti-citrillunated peptide antibody

*Mean BMI given for the 3 separate age groups 30-39, 40-49, 50-58. # Mean age for PR patients: 51.2 ± 11.3, healthy controls were age matched ± 5 years

2.3.7 Ultrasound machine and operator details

The ultrasound machine operators in studies had varying levels of experience, and results of reliability studies were not reported in all studies (see Table 2-10). Make and model of ultrasound machines varied, and the scanning protocols for obtaining ultrasound images included at least three different methods, with some centres using their own protocols instead of internationally recognised semi-quantitative grading systems.

Studies	Who scanned	Reliability	Ultrasound machine / probes	PD scanning settings	Scanning protocols
Micu et al. 2018[172]	Experienced senior physician		GE Logic S8; 9-15 MHz linear transducer	PRF 750 Hz Frequency 7 MHz	Wakefield 2005[96]
Machado et al. 2017[173]	Experienced radiologist	Inter-observer reliability - independent reviewers of 10% of images of selected joints	Esaote MyLab 60 Xvision; 6–18 MHz linear transducer	PRF 500-1000 Hz Frequency 6.3-10 MHz	Backhaus 2001[188] , Schmidt 2004[166], Szkudlarek 2003[136]
Manik et al. 2016[174]	Experienced musculoskeletal radiologist & a senior radiology registrar	SH : intraclass correlation coefficient (ICC) 0.944 (95% confidence interval of 0.934-0.952)	Philips IU22; 7-15 MHz hockey stick transducer	ND	Wakefield 2005[96]
Piga et al. 2016[175]	ND		Logiq9 (GE, Medical Systems, Wisconsin) 8–15MHz linear array probe	Torp-Pedersen 2008	Wakefield 2005[96]
Stewart et al. 2016[176]	Experienced musculoskeletal radiologist	2 musculoskeletal radiologists scored all the static images independently and blindly	Phillips iU22; 10 MHz linear transducer	PRF 400 - 500 Hz	ND
Fodor et al. 2015[178]	Team A: 2 experienced Rheumatologist sonographers Team B: 2 trainees with 4 hours teaching on MCP scanning	Independent and blind scanning of all subjects by team A and B, then results compared	Esaote MyLab 50; 18 MHz transducer	PRF 750 MHz.	Ellegaard 2007[186]
Amitai et al. 2015[177]	Experienced sonographer		Esaote Mylab Twice; 8–18 MHz linear transducer		Wakefield 2005,[96] Backhaus 2001,[188] 2002[189]
Hiraga et al. 2015[179]	Experienced musculoskeletal sonographer		Hitachi HI VISION Ascendus; 5–18 MHz linear transducer		own
Padovano et al. 2015[165]	Sonographer (2 years musculoskeletal ultrasound experience)		Esaote MyLab70 XVG; 6–18 MHz linear transducer	PRF 750Hz Minimum frequency 11MHz	Wakefield 2005[96]

Studies	Who scanned	Reliability	Ultrasound machine / probes	PD scanning settings	Scanning protocol
Cabrera-Villalba et al. 2014[180]	Experienced sonographer	Intra-rater reliability: 0.81 for SH and 0.92 for PDUS	Esaote My Lab 25; 8 -12 MHz transducer	PRF 500-800 Hz	Backhaus 2001,[188] Wakefield 2005[96]
Sant'Ana Petterle et al. 2013[181]	Experienced Rheumatologist sonographer	Good intra observer agreement for all joints	Esaote Mylab 30 CV; 6-8MHz linear transducer		ND
Witt et al. 2013[182]	ND	Inter-rater reliability 0.84 for SH, 0.93 for PD; intra-rater reliability 84.3 -90.4%	Esaote MyLab70; 8–18-MHz probe (small joints) 5–13-MHz probe (wrists).	PRF 750 MHz	Backhaus 2009,[190] Wakefield 2005[96]
Keen et al. 2011[183]	ND		Philips HDI 5000 sonoCT; 7-15 MHz hockey stick transducer	PRF 750 Hz	Wakefield 2005[96]
Millot et al. 2011[167]	Experienced sonographer		Esaote Mylab 70; 16 MHz linear probe	PRF 750 Hz Frequency 8.3 MHz	ND
Riente et al. 2009[184]	Experienced Rheumatologist sonographer (1 in each of 4 centres)	Inter-observer agreement 0.6-0.899	Logiq 9; 14 MHz linear probe		Wakefield 2005[96]
Hameed et al. 2008[185]	2 experienced musculoskeletal ultrasonographers		Philips HDI 5000; 7-15MHz hockey-stick transducer	PRF 700	Newman 1996,[191] Naredo 2005,[83] Szkudlarek 2003,[136] Weidekamm 2003[192]
Rosenburg et al. 2008[171]	2 Rheumatologists (2- 3 years musculoskeletal ultrasound experience)		Esaote TECHNOS MP, 10-13 MHz linear transducer	PRF 500MHz Frequency 8.3 MHz	Wakefield 2005[96]
Ellegaard et al. 2007[186]	Experienced musculoskeletal sonographer		Siemens Acuson Sequoia; 14 MHz linear transducer	n/a	Backhaus 2001,[188] and own
Schmidt et al. 2004[166]	Experienced physician sonographer	20 control images reviewed by another experienced trained physician sonographer	Esaote LA 523; 5-10 MHz transducer		Backhaus 2001[188]

Table 2-10 Details of sonographers, ultrasound machines and grading methods

ND, not documented; PRF, pulse repetition frequency

2.3.8 Ultrasound semi-quantitative grading or quantitative measurements used in studies

Thirteen studies used a semi-quantitative method of grading, nearly all of which (12/13) referenced Szkudlarek's 2003[136] grading of synovial hypertrophy and/or power Doppler (exclusively or in combination with other methods). Three studies used both semi-quantitative grading and measurements for synovial hypertrophy, and two used only a quantitative system (see Table 2-11).

Studies	grading or measurement	SH 0-3	SH grading method	PD 0-3	PD grading method
Micu et al. 2018[172]	grading	y	Szkudlarek 2003[136]	y	Szkudlarek 2003[136]
Machado et al. 2017[173]	grading and measurements	y	Szkudlarek 2003[136]	y	Szkudlarek 2003[136]
Manik et al. 2016[174]	grading and measurements	y	McNally 2008[193]	n/a	
Piga et al. 2016[175]	grading	y	Szkudlarek 2003,[136] Scheel 2005[137]	y	Szkudlarek 2003,[136] Scheel 2005[137]
Stewart et al. 2016[176]	grading	y	Szkudlarek 2003,[136] 2001[194]	y	Szkudlarek 2003,[136] 2001[194]
Amitai et al. 2015[177]	grading	y	Backhaus 2001,[188] 2002[189]	y	Backhaus 2001,[188] 2002[189]
Hiraga et al. 2015[179]	measurements				
Fodor et al. 2015[178]	grading and measurements	y	Szkudlarek 2003[136]	y	Backhaus 2009[190]
Padovano et al. 2015[165]	grading	y	Szkudlarek 2003[136]	y	Szkudlarek 2003[136]
Cabrera-Villalba et al. 2014[180]	grading	y	Szkudlarek 2003[136]	y	Szkudlarek 2003[136]
Sant'Ana Petterle et al. 2013[181]	grading	y	Szkudlarek 2003[136]	y	Filippucci 2004
Witt et al. 2013[182]	grading	y	Backhaus 2009,[190] Wakefield 2005[96]	y	Backhaus 2009,[190] Wakefield 2005[96]
Keen et al. 2011[183]	grading	y	Keen 2008[195]	y	Keen 2008[195]
Millot et al. 2011[167]	grading	y	Szkudlarek 2003[136]	y	Szkudlarek 2003[136]
Riente et al. 2009[184]	grading	y	Filippucci 2009,[196] Wakefield 2007,[197] Meenagh 2008[198]	y	Filippucci 2009,[196] Wakefield 2007,[197] Meenagh 2008,[198] Iagnocco 2008[199]
Hameed et al. 2008[185]	grading	y	Newman 1996,[191] Naredo 2005,[83] Szkudlarek 2003,[136] Weidekamm 2003[192]	y	Newman 1996,[191] Naredo 2005,[83] Szkudlarek 2003,[136] Weidekamm 2003[192]
Rosenburg et al. 2008[171]	grading and measurements	binary	Szudlarek 2003[136]	binary	Szudlarek 2003[136]
Ellegaard et al. 2007[186]	grading	0-4	Szkudlarek 2003,[136] 2004,[200] 2006,[90] Ostergaard 2005[201]	n/a	
Schmidt et al. 2004[166]	measurements				

Table 2-11 ultrasound grading systems and or/measurements used by each study

SH, synovial hypertrophy; PD, power Doppler; y, yes

2.3.9 Results of individual studies

There was high variability between studies regarding which joints (from MCPJs, PIPJs, wrists and MTPJs) were scanned; there was a complete set in only two studies (see Table 2-12). If all

studies scanned all 32 joints in all healthy subjects this would equal 38272 joints, instead of the total number of 21564 in these 19 papers.

Paper	N° of HS	MCPJs (n)	PIPJs (n)	Wrists (n)	MTPJs (n)
Machado et al. 2017# [173]	130	2 and 3 (520)	2 and 3 (520)	Yes (260)	1, 2 and 5 (780)
Manik et al. 2016[187]	30	2, 3 and 4 (180)			
Fodor et al. 2015[178]	50	2 and 5 (200)			
Keen et al. 2011[183]	20				1 to 5 (200)
Hameed et al. 2008[185]	25	1 to 5 (250)	1 to 5 (250)		
Schmidt et al.2004# [166]	102	2 (204)	2 (204)	Yes (204)	1 and 2 (408)
Micu et al. 2018 # [172]	75	1 to 5 (750)	2 to 5 (600)	Yes (150)	1 to 5 (750)
Stewart et al. 2016[176]	34				1 (68)
Piga et al. 2016# [175]	48	2 and 3 (192)		Yes (96)	
Padovano et al. 2015[165]	207	1 to 5 (2070)	1 to 5 (2070)	Yes (414)	1 to 5 (2070)
Amitai et al. 2015[177]	28		2 to 5 (224)		
Hiraga et al. 2015[179]	100				1 to 5 (1000)
Cabrera-Villalba et al. 2014[180]	30	1 to 5 (300)	1 to 5 (300)	Yes (60)	
Witt et al. 2013 [182]	30	1 to 5 (300)	1 to 5 (300)	Yes (60)	1 to 5 (300)
Sant'Ana Petterle et al. 2013# [181]	50				1 to 5 (500)
Millot et al. 2011 [167]	127	2 to 5 (1016)			1 to 5 (1270)
Rosenburg et al. 2008# [171]	46		2 to 5 (368)		
Riente et al. 2009# [184]	40	1 to 5 (400)	2 to 5 (320)		
Ellegaard et al. 2007# [186]	24*	1 to 5 (120)	1 to 5 (120)		
Total numbers	**1196**	**6502**	**5276**	**1244**	**7346**

Table 2-12 joints scanned in each study

HS, healthy subjects; MCPJs, metacarpophalangeal joints; PIPJs, proximal interphalangeal joints; MTPJs, metatarsophalangeal joints; n, number.
*All studies looked at bilateral joints except Ellegaard et al. 2007 which scanned dominant hand only
Studies also examined other joints and tendons with ultrasound

There were also differences in the aspects of the joints that were scanned, with the predominant view being dorsal, but some also included the palmar aspect, and even radial or ulnar. There were variations in documentation of longitudinal or transverse planes of view.

2.3.10 Synthesis of results

Relatively few of the studies had ultrasound data which could be compared for individual joints MCP 1-5 SH and PD grades ≥ 1 for the following reasons: some studies had not scanned all of these joints, some studies used measurements of SH, and some studies used a different threshold for abnormal and only stated SH or PD grades ≥ 2. There were low proportions of SH grade ≥ 1 in the MCP joints except for one study which only gave a relatively higher composite percentage of 21% for MCP1-5 SH grade ≥ 1 in HS (see Table 2-13). This is further highlighted as an outlier in the forest plot in Figure 2-2 to 2-4.

Study	Total number of joints	MCP 1 SH G ≥1 %	MCP 2 SH G ≥1 %	MCP 3 SH G ≥1 %	MCP 4 SH G ≥1 %	MCP 5 SH G ≥1 %
Micu et al. 2018[172]	150	2.67	3.5	3.5	3.5	3.5
Fodor et al. 2015[178]	50	ns	0	ns	ns	0
Padovano et al. 2015[165]	207	0.2	0.7	1.9	0.2	0
Witt et al. 2013[182]	30	21	21	21	21	21
Hameed et al. 2008[185]	25	1.2	1.2	1.2	1.2	1.2

Table 2-13 Percentage of metacarpophalangeal joints 1-5 with synovial hypertrophy grade ≥1

MCP, metacarpophalangeal; SH, synovial hypertrophy; G, grade; ns, not scanned

The majority of studies with SH grade ≥ 1 data for MCPJ 2, 3 and 5 had low prevalence at less than 5%, with a 95% confidence interval at less than 10% (Figures 2-2 to 2-4).

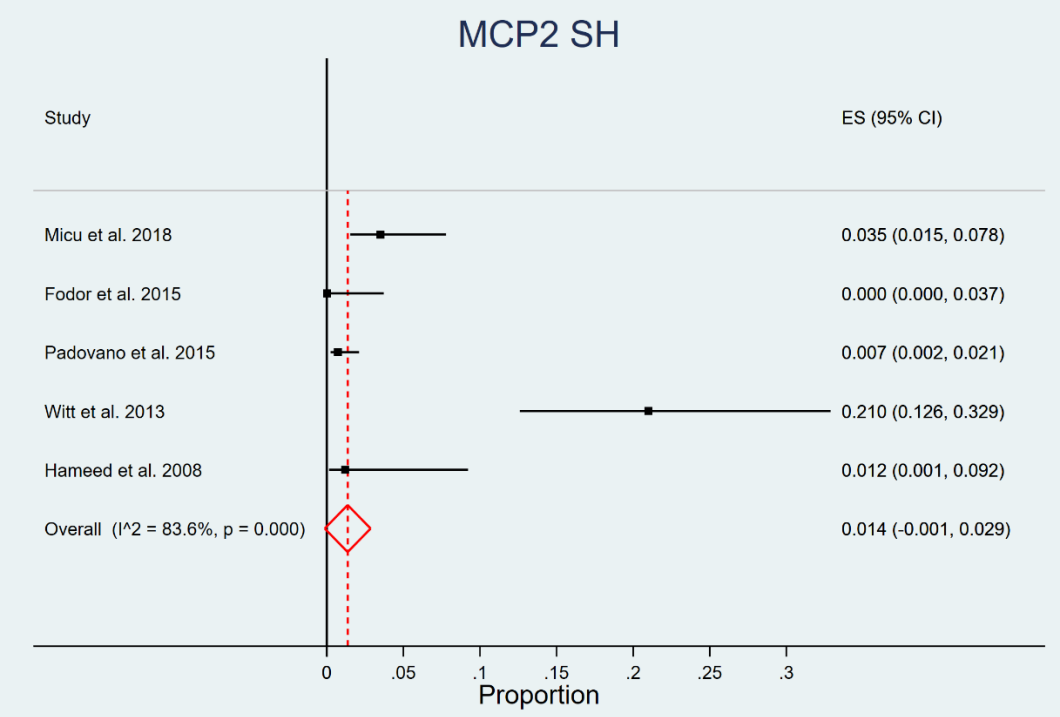

Figure 2-2 Forest plot showing proportion of healthy subjects with grade ≥ 1 synovial hypertrophy in second metacarpophalangeal joint

MCP, metacarpophalangeal joint; SH, synovial hypertrophy; ES, effect size; CI, confidence interval

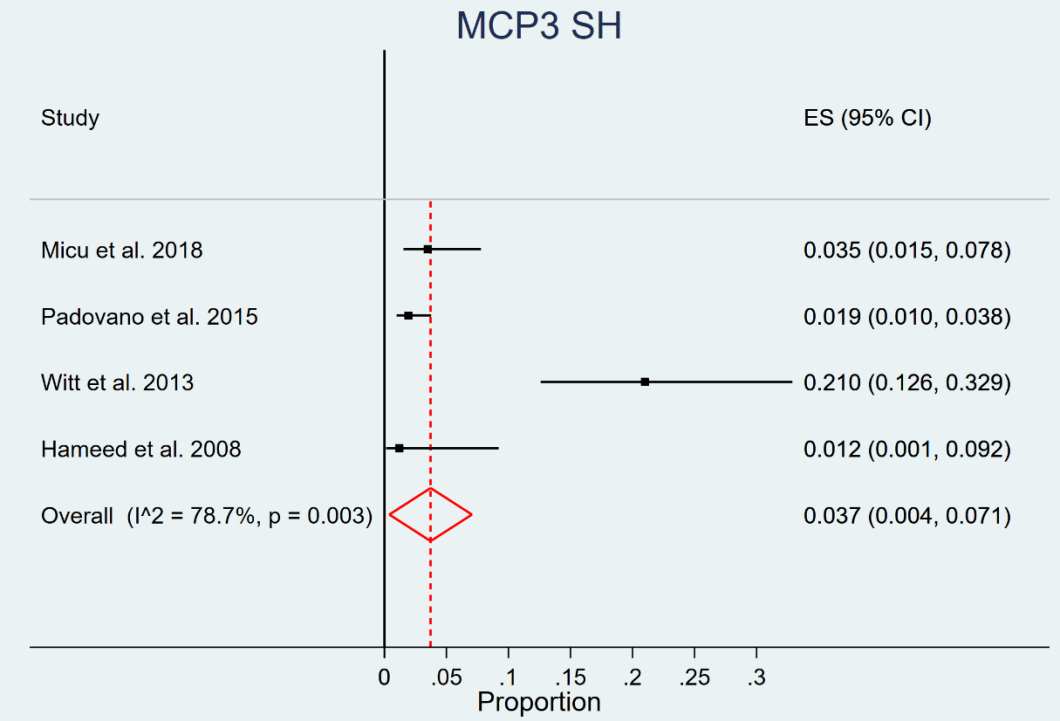

Figure 2-3 Forest plot showing proportion of healthy subjects with grade ≥1 synovial hypertrophy in third metacarpophalangeal joint

MCP, metacarpophalangeal joint; SH, synovial hypertrophy; ES, effect size; CI, confidence interval

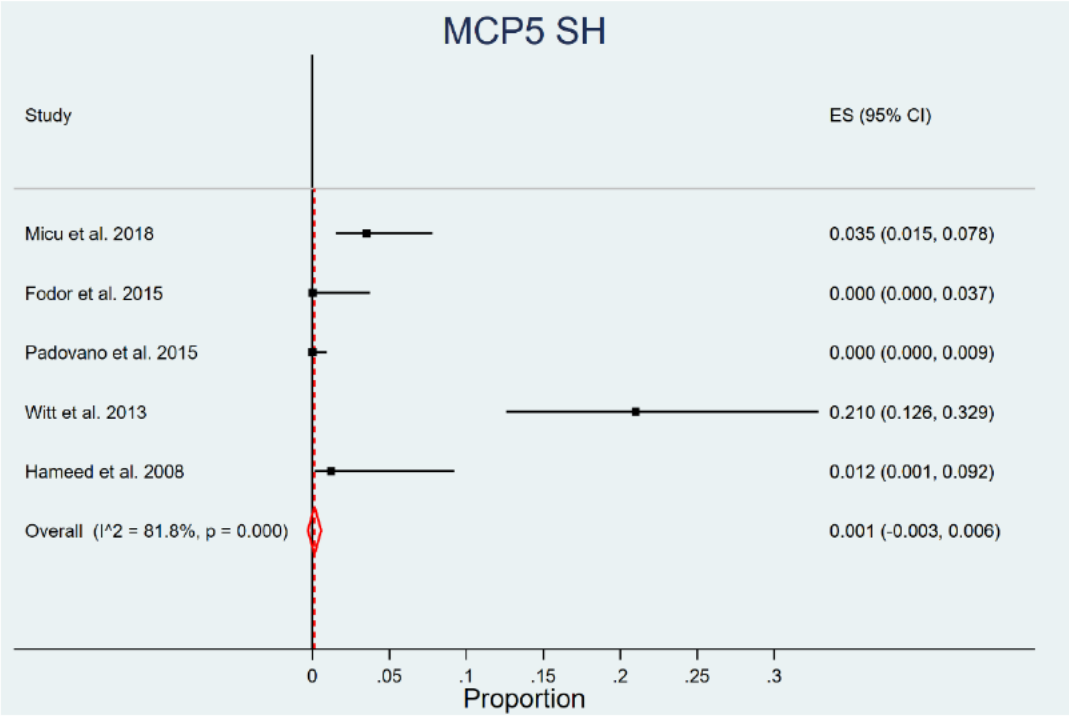

Figure 2-4 Forest plot showing proportion of healthy subjects with grade ≥1 synovial hypertrophy in fifth metacarpophalangeal joint

MCP, metacarpophalangeal joint; SH, synovial hypertrophy; ES, effect size; CI, confidence interval

When examining presence of grade ≥1 power Doppler, one study had given an overall percentage of PD grade ≥ 1 for MCP1-5 (see Table 2-14) and again, this was an outlier (Figures 2-5 to 2-7).

Studies	Total number of joints	MCP 1 PD G ≥1 %	MCP 2 PD G ≥1 %	MCP 3 PD G ≥1 %	MCP 4 PD G ≥1 %	MCP 5 PD G ≥1 %
Micu et al. 2018[172]	150	0.06	0.06	0.06	0.06	0.06
Machado et al. 2017[173]	260	ns	5	2.3	ns	ns
Piga et al. 2016[175]	96	ns	0	0	ns	ns
Fodor et al. 2015[178]	100	ns	2.5	ns	ns	2.5
Padovano et al. 2015[165]	414	0.2	0.2	0.2	ns	0
Cabrera-Villalba et al. 2014[180]	60	0	0	0	0	0
Millot et al. 2011[167]	254	ns	1.2	0.4	0	0.4
Hameed et al. 2008[185]	50	5.2	5.2	5.2	5.2	5.2

Table 2-14 Percentage of metacarpophalangeal joints 1-5 with Power Doppler grade ≥ 1

MCP, metacarpophalangeal; PD, Power Doppler; G, grade; ns, not scanned

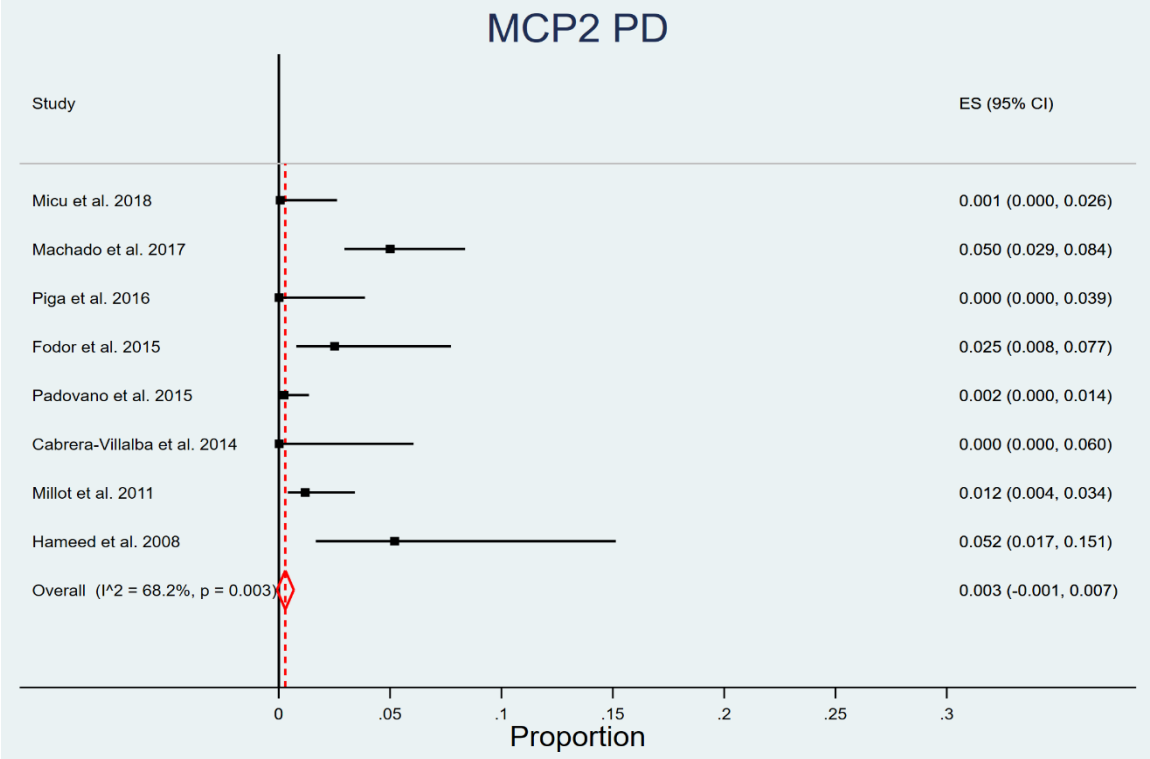

Figure 2-5 Forest plot showing proportion of healthy subjects with grade ≥ 1 power Doppler in second metacarpophalangeal joint

MCP, metacarpophalangeal joint; PD, Power Doppler; ES, effect size; CI, confidence interval

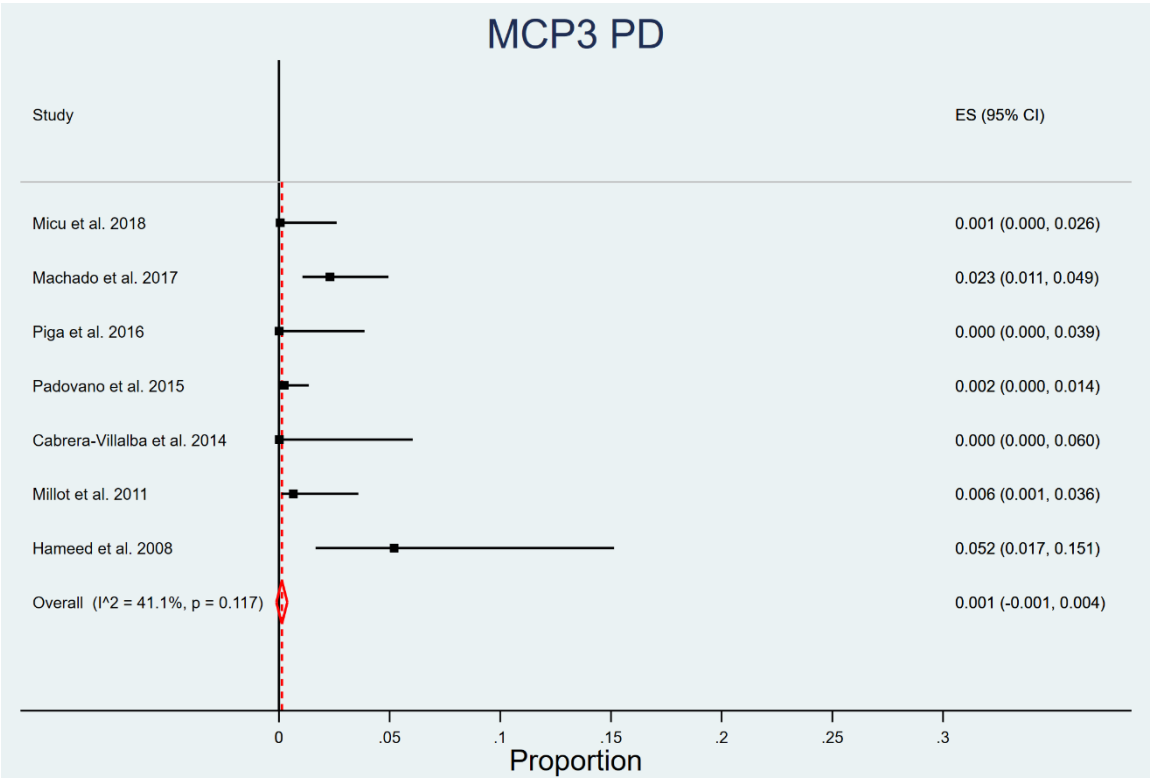

Figure 2-6 Forest plot showing proportion of healthy subjects with grade ≥ 1 power Doppler in third metacarpophalangeal joint

MCP, metacarpophalangeal joint; PD, Power Doppler; ES, effect size; CI, confidence interval

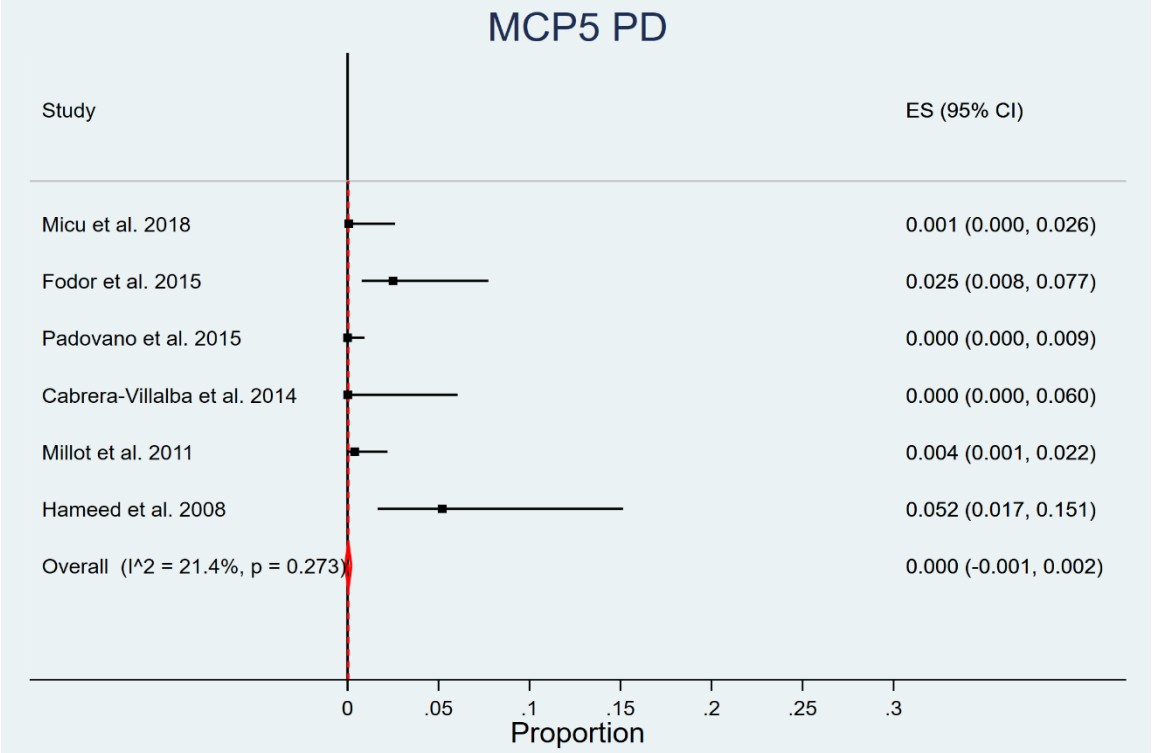

Figure 2-7 Forest plot showing proportion of healthy subjects with grade ≥ 1 power Doppler in fifth metacarpophalangeal joint

MCP, metacarpophalangeal joint; PD, Power Doppler; ES, effect size; CI, confidence interval

2.4 Discussion

2.4.1 Summary of evidence

This systematic literature review has highlighted that the current data available on the ultrasound of metacarpophalangeal, proximal interphalangeal, metatarsophalangeal and wrist joints in healthy subjects is very heterogeneous. Studies have used a range of different grading or measuring systems, and have been reported differently. Low proportions of SH and PD were seen in these joints in healthy subjects, but there was considerable variability between studies.

2.4.2 Limitations

This systematic review summarises data from very different studies with regards to what ultrasound changes are seen in the wrist, MCP, PIP and MTP joints of healthy controls. Because different measurements, grades or grade thresholds were used it is hard to accurately summarise and compare all these data.

The search terms were very specific with five search criteria needing to be filled, with the same search terms used for the three databases instead of MeSH or EMTREE for Medline and EMBASE respectively. This could potentially have missed some relevant papers. However, subsequent searches which broadened the ultrasound/ultrasonography/sonography search field yielded no more relevant non-duplicate abstracts.

The search criteria excluded non–English-language citations meaning some potentially interesting data may have been missed. Studies before the year 2000 were excluded because since then ultrasound technology has advanced with machines recording higher resolution images, meaning quality of images pre 2000 would be difficult to compare against those from more recent papers. Adults were included because ultrasound of joints in children with still forming joint structures is very different. Studies with less than 20 healthy subjects were excluded because smaller studies would be under-powered to draw any statistically significant conclusions, however in doing so we may have excluded some studies with important data on healthy subjects.

2.4.3 Assessment of quality of included studies

It was important that we included studies only where the controls were healthy. Some of the studies did not specify healthy subject inclusion/exclusion criteria. The details of ultrasound pathology recorded varied significantly between studies. One study included sciatica patients as healthy controls. Eleven studies used health care workers and the manual working population was underrepresented.

Most of the studies focussed primarily on inflammatory arthritis, and healthy subjects were a relatively smaller number of controls. It is possible controls were expected to have normal joints, so there may be under-reporting of ultrasound findings in the joints of healthy subjects.

2.5 Conclusions

The currently available data on ultrasound of hands, wrists and feet of healthy subjects are very heterogeneous, with studies using different definitions of healthy, different grading references and most studies not scanning all MCP, PIP, MTP and wrist joints. This has made it difficult to consolidate the data to give significant results. A large healthy control study is needed which uses one widely approved system of measuring ultrasound detected abnormalities in MCP, PIP, MTP and wrist joints.

3 ULTRASOUND OF HEALTHY SUBJECTS ACROSS THE AGE RANGE

I have included parts of the following chapter in a manuscript which was unpublished at the time of thesis first submission. The relevant text was written by me, with suggestions of revisions by my MD supervisors.

3.1 Introduction

3.1.1 Minimal disease

Musculoskeletal ultrasound (MSUS) is commonly and increasingly being used in clinical Rheumatology practice to predict, diagnose, and help guide management of inflammatory arthritis.[202] Ultrasound is more sensitive than clinical examination alone in detecting joint inflammation.[138] Advances in MSUS technology means that with higher resolution images very small or "minimal" abnormalities may be seen at the joint and tendon level. There is much recent research into the prevalence and significance of low disease activity or "minimal disease" of inflammatory arthritis seen on ultrasound which is often defined by low grades of ultrasound findings, such as synovial hypertrophy and power Doppler grade ≤ 1.[203 204]

There are instances where it is important to distinguish whether small or minimal abnormalities seen on ultrasound are physiological or pathological, for example in subjects in the older age range or in patients presenting with inflammatory features but no evidence of synovitis on clinical examination. The systematic literature review in Chapter 2 highlighted a need for a large study on healthy subjects to define what is normal, especially in the older age range because the age profile of incidence for Rheumatoid arthritis (RA) extends well into the 70's.

3.1.2 Healthy subjects

The highest incidence of RA occurs in the 5th to 7th decades[161] therefore it is important to know which joints are more likely to have positive findings in healthy subjects, particularly in older subjects. This has been published for MRI[152] but despite many years of validation exercises, no sufficiently powered study has been completed using MSUS.

On review of the currently available literature, studies on healthy subjects (HS) have found correlation between advancing age and positive findings seen on ultrasound of joints. The largest published study of MSUS of HS to date scanned 207 healthy subjects and found that 87.8% had at least one ultrasound abnormality, synovial effusion being the most prevalent. Metatarsophalangeal joint 1 (MTPJ1) was the most commonly affected, and the severity of joint ultrasound findings (synovial hypertrophy, power Doppler or synovial effusion) was predominantly grade 1.[165] However, the mean age of healthy subjects in this study was 35.5 years suggesting this study was underpowered to draw conclusions about the older population.

A small study of 24 healthy participants between 30 and 54 years old scanned metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the dominant hand. It found 89-95% of joints scored at least one abnormal grading; higher grades were associated with advance age; and were more common in women.[186]

3.1.3 Tendons

The musculoskeletal manifestations of Rheumatoid arthritis are commonly considered to be restricted to joints, which are the main focus of most clinical examinations and disease activity scoring systems. However tendons are often involved in early inflammatory arthritis,[147] and clinical examination alone may not detect tenosynovitis (TS).[148] The use of musculoskeletal

imaging such as ultrasound is more sensitive than clinical examination alone in detecting tenosynovitis[138] and TS seen on MSUS may be used to predict progression of early arthritis or flare in patients in clinical remission.[150 151]

The prevalence of ultrasound detected tendon abnormalities in healthy subjects is unknown, with the little available data in the literature compromising mainly of small studies which recruited healthy subjects as control cohorts for patients with rheumatic diseases. Many of these studies did not focus on HS within the age range of 40 to 70 years when RA may commonly present.[9]

3.2 Methods

3.2.1 Recruitment of healthy subjects

Adult healthy volunteers were recruited in centres with experience of participating in OMERACT (Outcome Measures in Rheumatology) ultrasound studies. Each of these centres was required to recruit at least 29 healthy volunteers according to the study protocol (see Appendix 1).

To ensure a wide range of age coverage, recruitment was obtained from a large variety of populations: university or hospital research staff, health service workers, students, volunteers from local advertising, friends and relatives of Rheumatology patients attending hospital clinic appointments. In the recruiting centre based at the Queen Elizabeth (QE) Hospital, Birmingham United Kingdom, the main focus of recruitment was an older age group targeted from the Birmingham 1000 Elders group.[205] This is a cohort of people over the age of 65 who volunteer to take part in various clinical trials requiring healthy older volunteers. Inclusion and exclusion criteria for this study are listed in Table 3-1.

Inclusion criteria
Age over 18 years old.
Exclusion criteria
Previous/current inflammatory joint disease (including crystal arthropathy)
VAS (visual analogue score) ≥ 10/100 on average in the past week for joint pain in hands, wrists or feet
Joint trauma in the last month, affecting areas that would be scanned.
Fulfilling ACR criteria for hand osteoarthritis (see Table 3-2)
Joint inflammation as clinically identified by a physician
Previous or current inflammatory bowel disease
History of culture-proven enteric and/or genitourinary infection in the last month
Current or previous corticosteroids use in the last 4 weeks.
Current non-steroidal anti-inflammatory use

Table 3-1 Inclusion and exclusion criteria for healthy subjects

Subjects were clinically examined to exclude inflammatory diseases, overt osteoarthritis (as defined by American College of Rheumatology (ACR) classification criteria for hand osteoarthritis, see Table 3-2), trauma, or current/recent use of medications that may confound the ultrasound findings. Metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP) and wrist joints were examined by an independent assessor in each centre and subjects were excluded if clinical evidence of synovitis was found.

Pain, aching or stiffness in the hand and:
Hard tissue enlargement of 2 or more of 10 selected joints*
Hard tissue enlargement of 2 or more DIPJs
Fewer than 3 swollen MCPJs
Deformity of at least 1 of 10 selected joints*

Table 3-2 American College of Rheumatology Classification Criteria for Osteoarthritis of the Hand [206]

DIPJ, distal interphalangeal joint; PIPJ, proximal interphalangeal joint; MCPJ, metacarpophalangeal joint; CMCJ, carpometacarpal joint
*the 10 selected joints are: 2nd and 3rd DIP, 2nd and 3rd PIP, 1st CMCJ of both hands

Ethical approval was obtained in each participating centre as per the requirements of each country. Healthy subjects gave written informed consent for recruitment to the study in the Birmingham centre, and again as per the requirements of each participating country.

3.2.2 Data collection

A clinical proforma was collected with the following information: age, gender, height, weight, BMI, history of skin psoriasis, history of previous joint replacement, family history of: osteoarthritis, skin psoriasis, inflammatory arthritis, connective tissue disease, inflammatory bowel disease. Social history information was collected including: hobbies that involve physical activity, occupation or last previous occupation if retired, smoking status and ethnic group.

In addition to the MCP, PIP, wrist and MTP joints being clinically examined by an independent assessor for synovitis, in the Birmingham centre a 66/68 joint count[81] for tenderness and swelling was conducted. Presence of osteoarthritis of the first MTP was assessed in all centres.

3.2.3 Ultrasound

An ultrasound assessment of the joints was performed in a temperature controlled radiology suite (see scanning protocol in Appendix 1), and blinded to the results of the independent clinical joint examination. A liberal amount of gel was used to avoid excessive compression of underlying structures. Details of the ultrasound machines and probes used, and the experience of the sonographers can be found in Table 3-3. Scans performed in Birmingham were by a trainee Rheumatology doctor with at least 2 years of ultrasound experience, firstly under direct, then indirect supervision of two Rheumatology physicians experienced in sonography.

Centre	Contributors	US exp (yrs)	US qualifications	Machine	Linear Transducer
Institute of Inflammation and Ageing, University of Birmingham, UK	Andrew Filer	15	EULAR teach the teacher, EULAR level 2	GE Logiq E9	8-18MHz; 6-15MHz
	Ilfita Sahbudin	9	MSc in Musculoskeletal Ultrasound, University of Bournemouth		
	Jeanette Trickey	6	BSR Basic Ultrasound Course		
University College London, UK	Coziana Ciurtin	10	EULAR level 2	GE Logiq E8	8-15MHz
Hôpital Ambroise Paré, Paris, France	Maria-Antonietta D'Agostino	25	EFSUMB level 3, EULAR level 2	ESAOTE MyLab70 XVG	6-18MHz PD 11 MHz, PRF 750Hz
	Hélène Gouze	6	French Musculoskeletal Ultrasound Course, EULAR Ultrasound intermediate Course		
Cliniques Universitaires Saint-Luc, Institut de recherche expérimentale et clinique (IREC), Université catholique de Louvain Bruxelles, Belgium.	Maria Stoenoiu	15	EFSUMB level 3, EULAR level 2	GE Logic E9	ML6-15, L8-18i.
	Mihaela Maruseac	5	EULAR intermediate course, EFSUMB level 2		
Ghent University, Belgium	Ruth Wittoek	15	EULAR level 2	ESAOTE MyLab 60	
	Philippe Carron	13	EULAR level 3		
University of Ferrara, Italy	Alessandra Bortoluzzi	12	Basic EULAR ultrasound course; advanced MSUS course endorsed by the Italian Society for Rheumatology	ESAOTE MyLab 70XVG	14–18 MHz
University of Ferrara, Italy	Georgios Filippou	20	EULAR level 2	Samsung RS80A	4-18 MHz; 3-12MHz
University of Pavia, Italy	Garifallia Sakellariou	11	none	ESAOTE Mylab 70 XVG	ESAOTE LA435 (6-18 MHz) PRF 0.75
Sacro Cuore Hospital, Negrar, Verona, Italy	Ilaria Tinazzi	16	EULAR intermediate ultrasound course	ESAOTE MyLabClassC	10-18 MHz PRF 750 Hz

Centre	Contributors	US exp (yrs)	US qualifications	Machine	Linear Transducer
Università degli Studi di Torino, Turin, Italy	Annamaria Iagnocco	37	EFSUMB level 3, EULAR level 2	ESAOTE MyLab8	L4-15 (4-15 MHz); LA435 (6-18MHz)
	Teodora Șerban	11	EFSUMB level 1, EULAR level 2, Romanian Ministry of Health Certified Sonographer		
	Irene Azzolin	5	Musculoskeletal Ultrasound in Rheumatology - EULAR Basic Course		
Copenhagen University Hospital, Denmark	Lene Terslev	22	EFSUMB level 3, EULAR level 2 Danish Rheumatology Association level 5	GE Logiq E9	ML 6-15 Colour Doppler (CD) frequency
	Mads Ammitzball Danielsen	10	EFSUMB level 2, EULAR level 1, Danish Rheumatology Association level 4		7.5 MHz, PRF 0.4
Aarhus University Hospital, Denmark	Ellen-Margrethe Hauge	16	Danish Rheumatology Association level 3	Hitachi Noblus	18-5 L64 Colour Doppler (CD) frequency
	Mads Nyhuus Bendix Rasch	10	Danish Rheumatology Association level 4		6.5 MHz
Diakonhjemmet Hospital, Oslo, Norway	Hilde Berner Hammer	20	EFSUMB level 3, EULAR level 2, EULAR faculty US courses	GE Logiq E9	6-15 MHz
Leiden University Medical Center, The Netherlands.	Marion Kortekaas	16	EULAR level 2 US level of the Dutch Rheumatology Association	GE logic E9	5-18 MHz
	Sarah Ohrndorf	14	EULAR level 2		
Pomeranian Medical University, Szczecin, Poland	Marcin Milchert	13	Certificates in Vascular Doppler Sonography and MS Sonography of Polish Ultrasonography Society and Polish Rheumatology Society	Phillips Epiq 5	18 MHz
	Jacek Fliciński	12	Level 1 EULAR MSUS Teach the Teacher Certificate of Proficiency Musculoskeletal Sonography Polish Rheumatological Society		

Centre	Contributors	US exp (yrs)	US qualifications	Machine	Linear Transducer
University of Vienna, Austria	Peter Mandl	16	EFSUMB level 3, EULAR level 2	GE S7	L8-18I
	Carina Borst	3	None		
Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania	Daniela Fodor	25	EFSUMB level 3, EULAR level 2	ESAOTE Mylab 25 Gold	18MHz
University of Medicine and Pharmacy, Craiova, Romania	Florentin Vreju	15	EULAR intermediate course, EULAR advanced course, EULAR teach-the-teachers course, EFSUMB	ESAOTE MyLab 7	3-18 MHz
Medical University of Plovdiv, Bulgaria.	Rositsa Karalilova	13	EULAR level 2, EULAR Certificate for Ultrasound Trainers in Rheumatology	GE Logiq E9	ML6-15 (6-15MHz)
Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain.	Esperanza Naredo	25	EFSUMB level 3, EULAR level 2	GE Logiq e	8-18 MHz
	Cesar Sifuentes-Cantu	5	Certifications by the Mexican College of Rheumatology,		
	Giuliana M.C. La Paglia	6	EULAR intermediate ultrasound course, EFSUMB level 1		
Instituto Nacional de Rehabilitacion, Mexico City, Mexico	Carlos Pineda	23	PANLAR level 3, ECOMER level 3	Hitachi Aloka F37	18 MHz
	Marwin Gutierrez	17	EFSUMB level 3, EULAR level 2, PANLAR level 3		
	Gustavo Leon	U	None declared		
	Cristina Reategui-Sokolova	6	None		

Centre	Contributors	US exp (yrs)	US qualifications	Machine	Linear Transducer
Zagazig University, Egypt	Mohamed Mortada	17	EULAR advanced course of musculoskeletal ultrasonography	HI VISION Avius	5-18 MHz PD frequency 7.5MHz, PRF 800Hz
Japanese Red Cross Medical Center, Tokyo, Japan	Takeshi Suzuki	17	EULAR intermediate, EULAR teach the teacher, JCR-certified sonographer	HI VISION Avius HI VISION Ascendus	EUP-L75 (5-18MHz)
Chiba University Hospital, Japan	Kei Ikeda	18	EULAR intermediate course, EULAR advanced course, EULAR teach-the-teachers course, JCR-certified sonographer	HI VISION Avius; HI VISION Ascendus	EUP-L75 (5-18MHz)

Table 3-3 Ultrasound machines and transducers used by centres

US, ultrasound; exp, experience; yrs, years, MHZ, megahertz; EULAR, European Alliance of Associations for Rheumatology, U, unknown

A multi-planar greyscale and power Doppler ultrasound examination of bilateral joints and tendon sites was performed in a systematic fashion, with views recorded according to European Alliance of Associations for Rheumatology (EULAR) standard reference scan guidelines.[188] Musculoskeletal specific pre-set parameters were used to optimise imaging for greyscale and power Doppler and reduce variability.

The following bilateral joints and tendons were scanned: dorsal metacarpophalangeal (MCP) joints 1-5; dorsal proximal interphalangeal joints (PIP) 1-5 (the interphalangeal joint of the thumb counted as PIPJ1); dorsal views of the wrists; dorsal metatarsophalangeal (MTP) joints 1-5; extensor carpi ulnaris (ECU) tendons; digit flexor (DF) tendons 1-5 (flexor pollicis longus counted as DF1, the deep and superficial digit flexor tendons at the level of the palmar MCPJs 2-5 counted as DF 2-5). Three view of the wrists were scanned (radio-, inter- and ulnar-carpal views) and the highest of these grades was documented as an overall grade for that joint.

An Outcome Measures in Rheumatology (OMERACT) ultrasound taskforce consensus defined system was used to assign these joints and tendons a grade between 0 and 3 for the following parameters: synovial hypertrophy (SH),[139 140] power Doppler (PD),[140 207] synovial effusion (EF),[162] osteophyte (Os),[208 209] tenosynovial hypertrophy (TSH),[210] and tenosynovial power Doppler (TPD).[210] The presence or absence of tenosynovial effusion (TEF)[210] and erosions (Er)[207] were also documented (see Table 3-4).

Ultrasound parameter and grades

Joints	SH	PD	EF	Os	Er
Metacarpophalangeal joints 1-5 (MCPJ 1-5)	0-3	0-3	0-3	0-3	Y/N*
Proximal interphalangeal joints 1-5 (PIPJ 1-5)	0-3	0-3	0-3	0-3	n/a
Wrist joints – composite of radiocarpal, intercarpal and ulnar carpal views (RC, IC, UC)	0-3	0-3	0-3	0-3	n/a
Metatarsophalangeal joints 1-5 (MTPJ 1-5)	0-3	0-3	0-3	0-3	Y/N*
Tendons	TSH	TPD	TEF		
Digit flexor tendons 1-5 (DF 1-5)	0-3	0-3	Y/N		
Extensor carpi ulnaris tendons (ECU)	0-3	0-3	Y/N		

Table 3-4 List of scanned joints and tendons, ultrasound parameters and gradings

SH, synovial hypertrophy; PD, power Doppler; EF, effusion; Os, osteophyte; Er, erosion; TSH, tenosynovial hypertrophy; TPD, power Doppler within the tendon sheath; TEF, tenosynovial effusion; Y/N, presence or absence of parameter recorded; n/a not applicable

*Erosions only documented in MCPJ 2, MCPJ 5 and MTPJ 5

3.2.4 Data cleaning

The ultrasound data were checked to exclude anomalous results. This included a PD score of 1 or more when the SH was graded 0 in that joint or tendon, because power Doppler should not be present if there is no hypertrophy of the synovial tissue. In these instances the centre responsible was asked to check the results, and if any doubt the PD was re-graded as 0.

3.2.5 Data variability

To minimise inter-operator variability, the first complete set of images from a scan of a healthy volunteer from each centre were reviewed by one experienced assessor in the Birmingham

centre to ensure that images of acceptable quality were being recorded. Any disagreement was then fed back to the centre and consensus achieved to ensure reliability in subsequent scans.

3.2.6 Generating wrist and metatarsophalangeal joint ultrasound atlases

To construct atlases containing ultrasound images of wrist and MTP atlases in healthy subjects, images of grade 0-3 SH for wrist radio-carpal (RC), inter-carpal (IC) and ulnar-carpal (UC), and MTP joints 1-5 were found from the healthy subjects recruited to the minimal disease study. Additionally, images for grade 2 and 3 SH in these joints were found in RA patients from the Birmingham Early Arthritis (BEACON) inception cohort database because they were rare in HS.

Images were reviewed and grouped initially in to: grade 0, grade 0+ (borderline images that could be considered grade 1 but should be graded as 0), grade 1, grade 1+ (borderline images that could be considered grade 2 but should be graded as 1), grade 2 and grade 3.

Images were reviewed by two experienced Rheumatology sonographers to confirm the correct grades. MTP 1 was considered as separate from MTP 2-5 because it is anatomically different from the other MTPJs. Similarly, separate images were selected for the RC, IC and UC wrist joints.

The initial wrist and MTPJ atlases were sent out to the rest of the collaborating ultrasound centres and feedback was received including disagreement of grading of images. Full consensus amongst the whole group was sought on the final version of the atlases.

3.2.7 Rheumatoid arthritis comparison cohort

Data for a comparison cohort of DMARD-naive patients presenting with RA fulfilling ACR-EULAR 2010[153] and/or 1987 criteria[41] at presentation were extracted from the Birmingham Early Arthritis (BEACON) inception cohort, which is managed by the research departments at the Queen Elizabeth and City Hospitals in Birmingham, United Kingdom. To be eligible for BEACON recruitment patients must be DMARD-naïve, have at least one clinically swollen joint, and had symptoms of inflammatory arthritis for less than three months. They have baseline clinical data, joint ultrasound data, serum, plasma, DNA, RNA, synovial fluid, synovium and cultured fibroblasts collected, with six monthly follow up for 2 years then annual follow up. The aim of this cohort is to investigate clinical features which may predict which patients go on to have resolution or persistence of symptoms, and predictive indicators of severity of inflammatory arthritis. The selected comparison cohort of RA patients underwent identical baseline tendon ultrasound assessment except the presence of TEF was not recorded. This RA cohort was used to compare with a group of age- and sex-matched (and where possible smoking status matched) healthy subjects selected from the larger HS cohort when analyzing the tendon data.

3.2.8 Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 26.0; IBM Corp. Armonk, NY, USA). Significance for the binary variable gender was assessed using Fisher's exact test. The continuous variables age and BMI (for all subjects) and early morning stiffness, CRP, joint counts (for RA patients) were not normally distributed; significance was therefore assessed using the Kruskall Wallis test. The joint and tendon gradings were dichotomised into either present (grade 1-3) or absent (grade 0). Kendall's tau-b correlation coefficient was used to compare the proportions of grade 1-3 SH, PD, Os, EF, TSH, TPD and

TEF between age groups in HS to examine if significance differences correlated with advancing age. Fisher's exact test was used to examine significance of difference in tendon gradings between HS and RA patients. McNemar's test was used to compare prevalence of right and left sided grade ≥ 1 ultrasound abnormalities because these data were paired from the same HS. Similarly McNemar's test was used to examine the prevalence of TSH within HS in different tendons, and to compare prevalence of TEF compared to TSH and TPD in HS tendons. Multiple testing was not corrected for.

Binary logistic regression analysis was performed to determine the effect of age, gender, BMI, manual occupation and smoking on the probability of HS having synovial hypertrophy grade ≥ 1 in MCP, PIP, MTP and wrist joints. The binomial dependent variable was SH grade 0 or ≥ 1. The categories of independent variables examined were gender (male or female), manual occupation (manual or non-manual worker) and smoking status (ever or never). The continuous independent variables were age and BMI. The Box Tidwell transformation was used to confirm non-linearity of the continuous independent variables age and BMI.

3.3 Initial ultrasound study of joints

3.3.1 Hypothesis

Low grades of synovial hypertrophy and power Doppler enhancement occur in the joints of healthy individuals in the older age range.

3.3.2 Objective

A large multi-centre ultrasound study of healthy subjects including the older age range to define what is normal on ultrasound.

3.3.3 Results

3.3.3.1 First round of recruitment

Adult healthy subjects (HS) were recruited between August 2017 and May 2018, yielding 543 HS after exclusions. These HS were recruited in 23 centres in 14 countries, and a list of centres, study contributors, ultrasound machines and probes are detailed in Table 3.3.

3.3.3.2 Second round of recruitment

Preliminary data from all centres were analysed and presented at the June 2018 OMERACT meeting in Sydney, Australia. At this meeting it was observed that the age range of volunteers was strongly biased towards younger age groups (Figure 3-1). This was likely due to younger volunteers more being more easily available at the places of work in the recruiting centres. A second round of recruitment targeting volunteers between the ages of 40 and 80 years old was launched. Between July 2018 and April 2019 according to the same protocol, 16/23 centres agreed to scan up to an extra 15 healthy recruits over the age of 40 years.

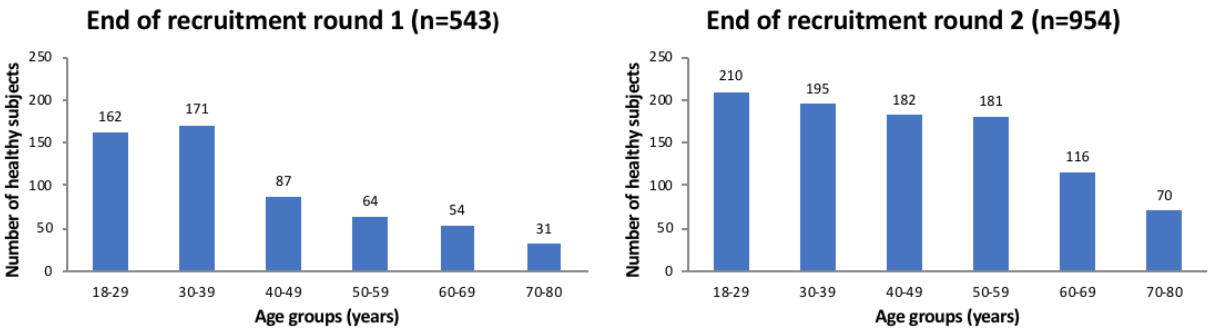

Figure 3-1 Age distribution of healthy subjects after first and second rounds of recruitment

By the end second round of recruitment which focussed on HS over the age of 40, there were similar proportions of HS in each age decade between 18 and 59. The older age groups (60-80 years old) still had lower numbers but were better represented (Figure 3-1).

3.3.3.3 Healthy subjects demographics

After both rounds of recruitment there were a total of 1049 adult HS. The final number was 954 after all exclusions which were are detailed in Figure 3-2. In addition to the 83 HS who were excluded due to missing data or meeting exclusion criteria, 12 HS were excluded during a data cleaning exercise before ultrasound data analysis because unforeseen conditions were identified which may have biased joint and tendon ultrasound results. One HS aged 85 years was excluded because they would have been the single member of an age group > 80 years old.

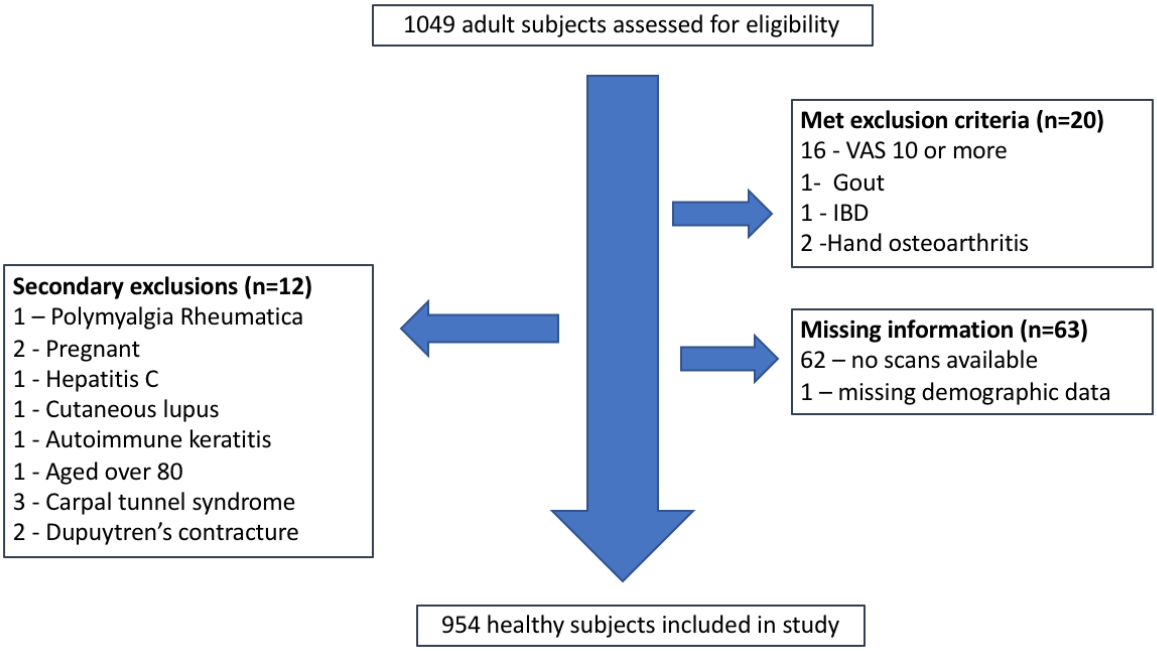

Figure 3-2 Flow diagram of recruitment and exclusions of healthy subjects
IBD, inflammatory bowel disease

The HS were divided in to three age groups in order to compare demographic and ultrasound data. These three groups were termed: young "Y" (18-39 years), middle "M" (40-59 years) and old "O" (60-80 years). The mean age of HS was 44.4 years (±15.5) with an age range of 18-80. Unintentionally a larger proportion of healthy females were recruited to this study (see Table 3-5). An explanation is that more females work in healthcare settings which would have been easily accessible for recruitment to the study. These occupations include: nurses, administrative staff, allied health care professionals and secretaries which accounted for 39.7% of the occupations of the HS. The largest proportion of female HS were in the 40-59 year old age group (81.5%). The proportion of genders amongst the volunteers from the Birmingham Healthy Elders Cohort was similar (48/90 female). The total proportion of HS females across all age groups was 681/954 (71.3%). RA affects more females than males with an incidence between 2 to 5:1 dependent on age,[211] therefore with regards to gender the HS group is representative of a control group for an RA cohort.

	HS Y 18-39 yr	HS M 40-59 yr	HS O 60-80 yr	HS Y/M/O p value
n	405	363	186	
Age, yr, median (IQR)	29 (25-33)	49 (44-54)	67 (62-72)	< 0.001
Females, n (%)	268 (66.2)	296 (81.5)	117 (62.9)	<0.001
BMI median (IQR)	22.2 (20.4, 24.5)	24.4 (21.6, 27.9)	24.8 (22.7, 27.7)	<0.001
Smoking never (%)	316 (78)	246 (67.8)	116 (62.4)	<0.001*
ever (%)	88 (21.7)	117 (32.3)	67 (36.1)	<0.001*
current (%)	47 (11.6)	62 (17.1)	12 (6.5)	0.006**
MCPJ 1 SH grade ≥1 n (%)	38 (4.7)	65 (9.0)	31 (8.4)	0.002
MCPJ 2 SH grade ≥1 n (%)	28 (3.5)	63 (8.7)	48 (12.9)	<0.001
MCPJ 3 SH grade ≥1 n (%)	16 (2.0)	39 (5.4)	38 (10.2)	<0.001
MCPJ 4 SH grade ≥1 n (%)	14 (1.7)	29 (4.0)	24 (6.5)	<0.001
MCPJ 5 SH grade ≥1 n (%)	9 (1.1)	22 (3.0)	14 (3.8)	0.002
PIPJ 1 SH grade ≥1 n (%)	5 (0.6)	31 (4.4)	17 (4.6)	<0.001
PIPJ 2 SH grade ≥1 n (%)	6 (0.7)	20 (2.8)	13 (3.5)	<0.001
PIPJ 3 SH grade ≥1 n (%)	9 (1.1)	19 (2.6)	18 (4.9)	<0.001
PIPJ 4 SH grade ≥1 n (%)	12 (1.5)	15 (2.1)	15 (4.0)	0.012
PIPJ 5 SH grade ≥1 n (%)	5 (0.6)	6 (0.8)	9 (2.4)	0.015
Wrist SH grade ≥1 n (%)	92 (11.4)	123 (17.6)	90 (24.9)	<0.001
MTPJ 1 SH grade ≥1 n (%)	288 (35.6)	290 (41.4)	194 (52.7)	<0.001
MTPJ 2 SH grade ≥1 n (%)	210 (25.9)	223 (31.9)	104 (28.3)	0.112
MTPJ 3 SH grade ≥1 n (%)	151 (18.6)	169 (24.1)	72 (19.6)	0.212
MTPJ 4 SH grade ≥1 n (%)	86 (10.6)	114 (16.3)	58 (15.8)	0.002
MTPJ 5 SH grade ≥1 n (%)	19 (2.3)	15 (2.1)	9 (2.4)	1.00
MCPJ 1 PD grade ≥1 n (%)	0 (0.0)	4 (0.6)	0 (0.0)	0.344
MCPJ 2 PD grade ≥1 n (%)	2 (0.2)	4 (0.6)	14 (3.8)	<0.001
MCPJ 3 PD grade ≥1 n (%)	3 (0.4)	2 (0.3)	9 (2.4)	0.002
MCPJ 4 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	5 (1.3)	<0.001
MCPJ 5 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	2 (0.5)	0.038
PIPJ 1 PD grade ≥1 n (%)	0 (0.0)	3 (0.4)	1 (0.3)	0.132
PIPJ 2 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	2 (0.5)	0.038
PIPJ 3 PD grade ≥1 n (%)	0 (0.0)	1 (0.1)	2 (0.5)	0.050
PIPJ 4 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	1 (0.3)	0.195
PIPJ 5 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	1 (0.3)	0.195
Wrist PD grade ≥1 n (%)	7 (0.9)	18 (2.6)	17 (4.7)	<0.001
MTPJ 1 PD grade ≥1 n (%)	8 (1.0)	23 (3.3)	18 (4.9)	<0.001
MTPJ 2 PD grade ≥1 n (%)	1 (0.1)	1 (0.1)	6 (1.6)	0.003
MTPJ 3 PD grade ≥1 n (%)	3 (0.4)	2 (0.3)	1 (0.3)	0.746
MTPJ 4 PD grade ≥1 n (%)	3 (0.4)	2 (0.3)	3 (0.8)	0.482
MTPJ 5 PD grade ≥1 n (%)	1 (0.1)	0 (0.0)	0 (0.0)	0.627

Table 3-5 Demographics and grade 1-3 synovial hypertrophy and power Doppler in scanned joints for healthy subjects

HS, healthy subjects; HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); IQR, interquartile range; BMI, body mass index; MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint; SH, synovial hypertrophy; PD, power Doppler.
*"never" compared to "ever" smokers. ** "current" compared to "never" smokers

The HS in the older two age groups had significantly higher BMIs than the 18-39 year old group ($p<0.001$). The youngest age group had a significantly more HS who had never smoked ($p<0.01$). These different demographics may have biased the ultrasound results seen in different age groups.

Older age was significantly associated with more grade ≥1 SH in all joints scanned ($p<0.05$) except MTPJ 2, 3 and 5 (see Table 3-5). There were low levels of Power Doppler present in all examined joints. The older age groups had significantly more PD grade ≥1 in MCPJ 1-5, PIPJ 2, wrists and MTPJ 1 and 2 ($p<0.05$). The joints with most prevalent PD grade ≥1 were MCPJ 2, MCPJ 3, the wrist and MTPJ 1, but this was still <5%. There were significantly more joints with PD grade ≥1 seen in the older age groups ($p<0.001$). Some of the above joints may be affected by mechanical loading, so more ultrasound joint findings might be expected in these particular joints in the older age groups. This is further examined in section 3.3.4.

3.3.3.4 Joint symmetry

For all ultrasound data analyses, the ultrasound grades recorded for left and right joints were counted as two grades at that joint level (e.g. right MCPJ 1 and left MCPJ 1 become two MCPJ 1 grades). The dominant hand side was not recorded for healthy subjects except for those recruited by the Birmingham centre, in which 88.9% (80/90) were right hand dominant. Figure 3-3 shows that when all ultrasound findings of grade ≥1 were considered, the number of abnormal joints was symmetrically distributed.

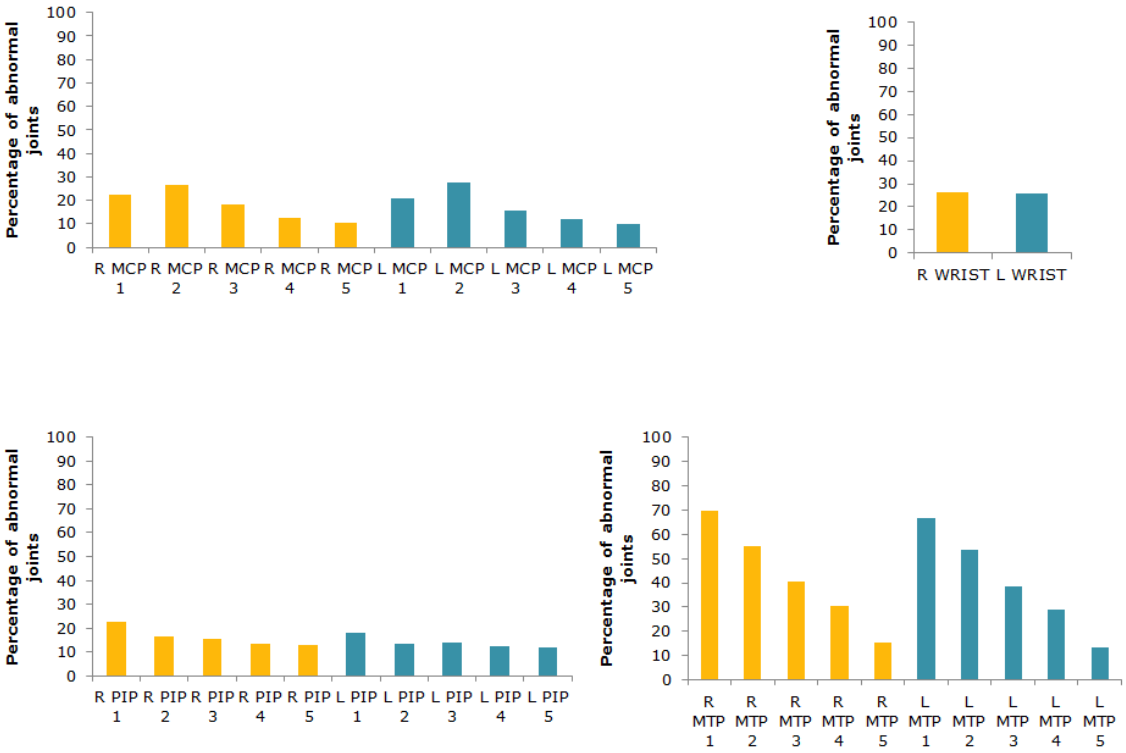

*Figure 3-3 Percentage of right and left joints with any ultrasound abnormality grade ≥ 1 **

*This included including synovial hypertrophy, power Doppler, effusion, osteophyte, erosion, tenosynovial hypertrophy, tenosynovial power Doppler and tenosynovial effusion)
R, right; L left; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint

The symmetry of the joints was further examined by comparing grade ≥1 MSUS abnormalities at each joint level and by each ultrasound parameter. The following tables compare grade ≥1 abnormalities for SH, PD, EF and Os, and Er (which was recorded as either present or absent) between left and right joints for all HS. (Tables 3-6 to 3-10).

When comparing synovial hypertrophy between left and right joints there were no significant differences except in two joints (Table 3-6), with significantly more ultrasound detected SH grade ≥1 in right sided MCPJ 2 (p=0.029) and right sided MTPJ1 (p=0.021) when all HS were examined irrespective of age group. Although the dominant hand was not recorded in most centres, it is likely most HS were right hand dominant, therefore the significantly higher prevalence of grade ≥1 SH in MCPJ 2 and MTPJ 1 likely represents more mechanical loading through these joints through right sided dominance.

	HS Y (18-39 yrs) grade ≥ 1		HS M (40-59 yrs) grade ≥ 1		HS O (60-80 yrs) grade ≥ 1		All age groups grade ≥ 1		
	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	All age groups L vs R p value*
MCPJ 1	19 (4.7)	19 (4.7)	26 (7.2)	39 (10.7)	16 (8.6)	15 (8.1)	61 (6.4)	73 (7.7)	0.224
MCPJ 2	16 (4.0)	12 (3.0)	25 (6.9)	38 (10.5)	19 (10.2)	29 (15.7)	60 (6.3)	79 (8.3)	0.029
MCPJ 3	6 (1.5)	10 (2.5)	17 (4.7)	22 (6.1)	19 (10.2)	19 (10.3)	42 (4.4)	51 (5.4)	0.289
MCPJ 4	8 (2.0)	6 (1.5)	16 (4.4)	13 (3.6)	7 (3.8)	17 (9.2)	31 (3.2)	36 (3.8)	0.568
MCPJ 5	7 (1.7)	2 (0.5)	10 (2.8)	12 (3.3)	7 (3.8)	7 (3.8)	24 (2.5)	21 (2.2)	0.743
PIPJ 1	1 (0.2)	4 (1.0)	16 (4.6)	15 (4.3)	6 (3.3)	11 (6.0)	23 (2.4)	30 (3.2)	0.337
PIPJ 2	4 (1.0)	2 (0.5)	8 (2.2)	12 (3.3)	7 (3.8)	6 (3.2)	19 (2.0)	20 (2.1)	1.000
PIPJ 3	4 (1.0)	5 (1.2)	9 (2.5)	10 (2.8)	7 (3.8)	11 (5.9)	20 (2.1)	26 (2.7)	0.362
PIPJ 4	3 (0.7)	9 (2.2)	9 (2.5)	6 (1.7)	5 (2.7)	10 (5.4)	17 (1.8)	25 (2.6)	0.215
PIPJ 5	3 (0.7)	2 (0.5)	5 (1.4)	1 (0.3)	2 (1.1)	7 (3.8)	10 (1.0)	10 (1.0)	1.000
Wrist	47 (11.6)	45 (11.1)	61 (17.4)	62 (17.7)	40 (22.1)	50 (27.6)	148 (15.8)	157 (16.8)	0.491
MTPJ 1	142 (35.1)	146 (36.0)	136 (39.8)	154 (44.0)	90 (48.9)	104 (56.5)	368 (39.2)	404 (43.0)	0.021
MTPJ 2	100 (24.7)	110 (27.2)	120 (34.3)	103 (29.4)	53 (28.8)	51 (27.7)	273 (29.1)	264 (28.1)	0.565
MTP 3	73 (18.0)	78 (19.3)	91 (26.0)	78 (22.3)	33 (17.9)	39 (21.2)	197 (21.0)	195 (20.8)	0.936
MTPJ 4	38 (9.4)	48 (11.9)	62 (17.7)	52 (14.9)	28 (15.2)	30 (16.9)	128 (13.6)	130 (13.8)	0.926
MTPJ 5	9 (2.2)	10 (2.5)	7 (2.0)	8 (2.3)	5 (2.7)	4 (2.2)	22 (2.3)	21 (2.3)	1.000

Table 3-6 Distribution ultrasound findings of synovial hypertrophy grade ≥ 1 in left and right joints in healthy subjects

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint; SH, synovial hypertrophy; * McNemar's test

There were no significant differences between left and right joints when analysing power Doppler (Table 3-7). Prevalence of PD grade ≥1 was low at less than 3%, except for two joint levels in the HS O (60-80 years) age group. In this oldest age group wrist PD grade ≥1 prevalence was higher in right wrist compared to the left wrist, and in the right MTPJ 1 compared to left MTPJ 1, but these were not statistically significant (p=0.184, p=0.06 respectively, McNemar's test).

	HS Y (18-39 yrs) grade ≥ 1		HS M (40-59 yrs) grade ≥ 1		HS O (60-80 yrs) grade ≥ 1		All age groups grade ≥ 1		
	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	All age groups L vs R p value*
MCP 1	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.2)	1.000
MCPJ 2	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.5)	6 (3.2)	1 (0.1)	8 (0.8)	0.454
MCPJ 3	1 (0.2)	2 (0.5)	0 (0.0)	2 (0.6)	4 (2.2)	5 (2.7)	5 (0.5)	9 (0.9)	0.388
MCPJ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (1.6)	2 (0.2)	3 (0.3)	1.000
MCPJ 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.2)	0 (0.0)	n/a
PIPJ 1	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	1 (0.5)	0 (0.0)	2 (0.2)	2 (0.2)	1.000
PIPJ 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.1)	1 (0.1)	1.000
PIPJ 3	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.1)	2 (0.2)	1.000
PIPJ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)	n/a
PIPJ 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)	n/a
Wrist	3 (0.7)	4 (1.0)	7 (2.0)	11 (3.1)	6 (3.3)	11 (6.1)	16 (1.7)	26 (2.8)	0.099
MTPJ 1	5 (1.2)	3 (0.7)	9 (2.6)	14 (4.0)	7 (3.8)	11 (6.0)	21 (2.2)	28 (3.0)	0.349
MTPJ 2	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	4 (2.2)	2 (1.1)	5 (0.5)	3 (0.3)	0.687
MTPJ 3	1 (0.2)	1 (0.5)	0 (0.0)	2 (0.6)	1 (0.5)	0 (0.0)	2 (0.2)	4 (0.4)	0.625
MTPJ 4	1 (0.2)	2 (0.5)	1 (0.3)	1 (0.3)	2 (1.1)	1 (0.5)	4 (0.4)	4 (0.4)	1.000
MTPJ 5	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	n/a

Table 3-7 Distribution ultrasound findings of Power Doppler grade ≥ 1 in left and right joints in healthy subjects

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint; PD, Power Doppler; * McNemar's test

The joints which had significantly higher right-sided prevalence of grade ≥ 1 effusion were PIPJ 1 ($p<0.001$), and to a lesser degree of significance PIPJ 3 ($p=0.016$). (Table 3-8).

	HS Y (18-39 yrs) grade ≥ 1		HS M (40-59 yrs) grade ≥ 1		HS O (60-80 yrs) grade ≥ 1		All age groups grade ≥ 1		
	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	All age groups L vs R p value*
MCPJ 1	32 (7.9)	25 (6.2)	38 (10.5)	37 (10.2)	30 (16.1)	33 (17.8)	100 (10.5)	95 (10.0)	0.727
MCPJ 2	25 (6.2)	25 (6.2)	45 (12.4)	39 (10.7)	36 (19.4)	33 (17.8)	106 (11.1)	97 (10.2)	0.463
MCPJ 3	21 (5.2)	28 (6.9)	33 (9.1)	26 (7.2)	22 (11.8)	22 (11.9)	76 (8.0)	76 (8.0)	1.000
MCPJ 4	22 (5.4)	21 (5.2)	28 (7.7)	24 (6.6)	23 (12.4)	22 (11.9)	73 (7.7)	67 (7.0)	0.606
MCPJ 5	5 (1.2)	8 (2.0)	21 (5.8)	16 (4.4)	16 (8.6)	15 (8.1)	39 (4.1)	42 (4.4)	0.798
PIPJ 1	37 (9.1)	57 (14.1)	36 (10.3)	52 (14.9)	21 (11.4)	31 (16.9)	94 (10.0)	140 (14.9)	<0.001
PIPJ 2	12 (3.0)	15 (3.7)	16 (4.4)	19 (5.2)	10 (5.4)	14 (7.6)	38 (4.0)	48 (5.0)	0.193
PIPJ 3	10 (2.5)	20 (4.9)	13 (3.6)	18 (5.0)	10 (5.4)	14 (7.6)	33 (3.5)	52 (5.5)	0.016
PIPJ 4	9 (2.2)	17 (4.2)	12 (3.30	12 (3.3)	14 (7.5)	13 (7.0)	35 (3.7)	42 (4.4)	0.392
PIPJ 5	10 (2.5	12 (3.0)	11 (3.0)	17 (4.7)	11 (5.9)	9 (4.9)	32 (3.4)	38 (4.0)	0.461
Wrist	58 (14.3)	59 (14.6)	51 (14.6)	46 (13.1)	19 (10.5)	26 (14.4)	128 (13.7)	131 (14.0)	0.869
MTPJ 1	219 (54.1)	230 (56.8)	161 (46.0)	161 (46.0)	98 (53.3)	115 (62.5)	478 (50.9)	506 (53.9)	0.105
MTPJ 2	153 (37.8)	163 (40.2)	126 (36.0)	129 (36.9)	65 (35.3)	69 (37.5)	344 (36.6)	361 (38.4)	0.314
MTPJ 3	93 (23.0)	107 (26.4)	100 (28.6)	101 (28.9)	51(27.7)	63 (34.2)	244 (26.0)	271 (28.9)	0.080
MTPJ 4	70 (17.3)	83 (20.5)	71 (20.3)	77 (22.0)	43 (23.4)	46 (25.0)	184 (19.6)	206 (21.9)	0.113
MTPJ 5	22 (5.4)	27 (6.7)	22 (6.3)	30 (8.6)	9 (4.9)	9 (4.9)	53 (5.6)	66 (7.0)	0.171

Table 3-8 Distribution ultrasound findings of presence of effusion in left and right joints in healthy subjects

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint; EF, effusion; * McNemar's test

The higher prevalence of grade ≥1 EF in PIPJ 1 and PIPJ 3 in the right hands of HS may physiological, related to more activity or weight-loading through these right-sided joints. Another explanation may be degenerative changes in these joints, but there were no significant differences in prevalence of osteophytes between left and right hands in in PIPJ 1 or PIPJ 3 (Table 3-9). The only joint with significant difference in prevalence of grade ≥1 osteophytes between left and right sides was MTPJ 1 (p=0.013).

	HS Y (18-39 yrs) grade ≥ 1		HS M (40-59 yrs) grade ≥ 1		HS O (60-80 yrs) grade ≥ 1		All age groups grade ≥ 1		
	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	All age groups L vs R p value*
MCPJ 1	10 (2.6)	17 (4.4)	41 (11.6)	44 (12.5)	38 (20.9)	35 (19.9)	89 (9.6)	96 (10.4)	0.555
MCPJ 2	30 (7.7)	33 (8.5)	77 (21.9)	71 (20.2)	42 (23.1)	36 (19.9)	149 (16.1)	140 (15.2)	0.543
MCPJ 3	14 (3.6)	15 (3.8)	39 (11.1)	43 (12.2)	17 (9.3)	20 (11.0)	70 (7.6)	78 (8.5)	0.461
MCPJ 4	7 (1.8)	10 (2.6)	21 (6.0)	19 (5.4)	7 (3.8)	10 (9.6)	35 (3.8)	39 (4.2)	0.659
MCPJ 5	15 (3.8)	13 (3.3)	28 (8.0)	22 (6.3)	6 (3.3)	12 (6.6)	49 (5.3)	47 (5.1)	0.894
PIPJ 1	13 (3.3)	5 (1.3)	37 (10.9)	44 (13.0)	43 (23.9)	51 (28.5)	93 (10.2)	100 (11.0)	0.461
PIPJ 2	23 (5.9)	17 (4.4)	50 (14.2)	62 (17.6)	28 (15.4)	34 (18.8)	101 (10.9)	113 (12.2)	0.208
PIPJ 3	16 (4.1)	17 (4.4)	56 (15.9)	54 (15.3)	29 (15.9)	31 (17.1)	101 (10.9)	102 (11.1)	0.916
PIPJ 4	15 (3.8)	21 (5.4)	50 (14.2)	42 (11.9)	23 (12.6)	27 (14.9)	88 (9.5)	90 (9.8)	0.807
PIPJ 5	25 (6.4)	18 (4.6)	37 (10.5)	40 (11.4)	28 (15.4)	31 (17.1)	90 (9.7)	89 (9.6)	1.000
Wrist	1 (0.3)	2 (0.5)	13 (3.8)	6 (1.8)	8 (4.5)	11 (6.2)	22 (2.4)	19 (2.1)	0.676
MTPJ 1	8 (2.1)	10 (2.6)	48 (14.2)	55 (16.2)	62 (34.4)	80 (44.4)	118 (13.0)	145 (16.0)	0.013
MTPJ 2	20 (5.1)	11 (2.8)	30 (8.8)	36 (10.6)	17 (9.4)	15 (8.3)	67 (7.4)	62 (6.8)	0.625
MTPJ 3	9 (2.3)	5 (1.3)	16 (4.7)	19 (5.6)	8 (4.4)	9 (5.0)	33 (3.6)	33 (3.6)	1.000
MTPJ 4	8 (2.1)	6 (1.5)	19 (5.6)	17 (5.0)	9 (5.0)	10 (5.6)	36 (4.0)	33 (3.6)	0.711
MTPJ 5	16 (4.1)	24 (6.2)	33 (9.7)	29 (8.6)	16 (8.9)	22 (12.2)	65 (7.2)	75 (8.3)	0.275

Table 3-9 Distribution ultrasound findings of osteophyte grade ≥ 1 in left and right joints in healthy subjects

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint; Os, osteophyte; * McNemar's test

The prevalence of erosions detected was low, and there were no significant differences between left and right joints (Table 3-10).

	HS Y (18-39 yrs) present		HS M (40-59 yrs) present		HS O (60-80 yrs) present		All age groups present		
	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	Left n (%)	Right n (%)	All age groups L vs R p value*
MCPJ 2	4 (1.0)	0 (0.0)	3 (0.9)	2 (0.6)	2 (1.1)	5 (2.8)	9 (1.0)	7 (0.8)	0.774
MCPJ 5	3 (0.8)	3 (0.7)	0 (0.0)	4 (1.1)	1 (0.6)	1 (0.5)	4 (0.4)	8 (0.8)	0.344
MTPJ 5	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.8)	0 (0.0)	1 (0.5)	2 (0.2)	4 (0.4)	0.687

Table 3-10 Distribution ultrasound findings of presence of erosion in left and right joints in healthy subjects

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); Er, erosion; MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joint; MTPJ, metatarsophalangeal joint * McNemar's test

In summary, there were few significant difference between the left and right joints, with those significantly more prevalent ultrasound abnormalities in the right-sided joints attributable to greater mechanical load.

3.3.4 Ultrasound findings in joints across the age groups

The ultrasound abnormalities of grade 1 to 3 synovial hypertrophy, power Doppler and joint effusion were analysed, irrespective of right or left side, in each of the three age groups: HS Y (young, 18 to 39 year olds), HS M (middle, 40 to 59 year olds) and HS O (old, 60 to 80 year olds).

3.3.4.1 Metacarpophalangeal joints

There were significantly more grade ≥1 synovial hypertrophy in the metacarpophalangeal joints in the older age groups ($p < 0.005$) (Table 3-11). Grade 3 SH was not seen in the MCPJs of HS in the younger age group, and was rarely seen only in MCPJ 1 and 2 in the middle and older two age groups (<1%) (Table 3-12). Prevalence of grade 2 SH was higher in the HS O age

group compared to the HS M age group. Therefore, the prevalence and severity of SH appears to increase with age in the MCPJs. This can be visualised in the column charts in Figure 3-4.

	HS Y (18-39 years) grade ≥ 1	HS M (40-59 years) grade ≥ 1	HS O (60-80 years) grade ≥ 1	p value* HS Y vs M vs O G ≥1
SH				
MCPJ 1	38 (4.7)	65 (9.0)	31 (8.4)	0.002
MCPJ 2	28 (3.5)	63 (8.7)	48 (12.9)	<0.001
MCPJ 3	16 (2.0)	39 (5.4)	38 (10.2)	<0.001
MCPJ 4	14 (1.7)	29 (4.0)	24 (6.5)	<0.001
MCPJ 5	9 (1.1)	22 (3.0)	14 (3.8)	0.002
PD				
MCPJ 1	0 (0.0)	4 (0.6)	0 (0.0)	0.344
MCPJ 2	2 (0.2)	4 (0.6)	14 (3.8)	<0.001
MCPJ 3	3 (0.4)	2 (0.3)	9 (2.4)	0.002
MCPJ 4	0 (0.0)	0 (0.0)	5 (1.3)	<0.001
MCPJ 5	0 (0.0)	0 (0.0)	2 (0.5)	0.038
EF				
MCPJ 1	57 (7.0)	75 (10.3)	63 (16.9)	<0.001
MCPJ 2	50 (6.2)	84 (11.6)	69 (18.6)	<0.001
MCPJ 3	49 (6.0)	59 (8.1)	44 (11.8)	0.001
MCPJ 4	43 (5.3)	52 (7.2)	45 (12.2)	<0.001
MCPJ 5	13 (1.6)	37 (5.1)	31 (8.3)	<0.001

Table 3-11 Ultrasound findings grade ≥ 1 in metacarpophalangeal joints in healthy subjects according to age group

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCPJ, metacarpophalangeal joint;; G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion; * Kendall's tau-b test

The prevalence of power Doppler in the MCPJs was low across all the age groups but significantly higher in MCPJ 2-5 in the older age groups ($p<0.05$) (Table 3-11, Figure 3-4). MCPJ 2, 3 and 4 in the HS O age group had the most frequent PD abnormalities of grade 1 PD at 3.5%, 1.9% and 1.3% respectively, with the prevalence of PD grade ≥ 1 less than 1% in all the other age groups (Table 3-12). Most power Doppler was of grade 1 severity.

	HS Y (18-39 years)			HS M (40-59 years)			HS O (60-80 years)		
	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)
SH									
MCPJ 1	33 (4.1)	5 (0.6)	0 (0.0)	44 (6.1)	18 (2.3)	3 (0.4)	18 (4.9)	10 (2.7)	3 (0.8)
MCPJ 2	27 (3.3)	1 (0.1)	0 (0.0)	55 (7.6)	7 (1.0)	1 (0.1)	34 (9.2)	14 (3.8)	0 (0.0)
MCPJ 3	13 (1.6)	3 (0.4)	0 (0.0)	36 (5.0)	3 (0.4)	0 (0.0)	29 (7.8)	15 (0.8)	0 (0.0)
MCPJ 4	13 (1.6)	1 (0.1)	0 (0.0)	22 (3.0)	7 (1.0)	0 (0.0)	19 (5.1)	5 (1.3)	0 (0.0)
MCPJ 5	7 (0.9)	2 (0.2)	0 (0.0)	21 (2.9)	1 (0.1)	0 (0.0)	10 (2.7)	4 (1.1)	0 (0.0)
PD									
MCPJ 1	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MCPJ 2	2 (0.2)	0 (0.0)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)	13 (3.5)	1 (0.3)	0 (0.0)
MCPJ 3	3 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	7 (1.9)	2 (0.5)	0 (0.0)
MCPJ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	0 (0.0)	0 (0.0)
MCPJ 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
EF									
MCPJ 1	55 (6.8)	2 (0.2)	0 (0.0)	70 (9.6)	5 (0.7)	0 (0.0)	58 (15.6)	5 (1.3)	0 (0.0)
MCPJ 2	50 (6.2)	0 (0.0)	0 (0.0)	77 (10.6)	7 (1.0)	0 (0.0)	62 (16.7)	7 (1.9)	0 (0.0)
MCPJ 3	48 (5.9)	1 (0.1)	0 (0.0)	56 (7.7)	3 (0.4)	0 (0.0)	42 (11.3)	2 (0.5)	0 (0.0)
MCPJ 4	42 (5.2)	1 (0.1)	0 (0.0)	48 (6.6)	4 (0.6)	0 (0.0)	44 (11.9)	1 (0.3)	0 (0.0)
MCPJ 5	12 (1.5)	1 (0.1)	0 (0.0)	33 (4.5)	4 (0.6)	0 (0.0)	29 (7.8)	2 (0.5)	0 (0.0)

Table 3-12 Ultrasound findings of synovial hypertrophy, power Doppler and effusion of grade 1 to 3 in metacarpophalangeal joints in healthy subjects according to age groups

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion

The prevalence of MCP joint effusion was significantly higher than SH and PD ($p < 0.001$), with all joints except MCPJ 5 in the youngest age group having grade ≥ 1 effusion in more than 5% of HS (see line at 5% for EF in Figure 3-4). MCPJ 1-5 EF grade ≥ 1 was significantly more prevalent in the older age groups ($p<0.001$, Table 3-11).

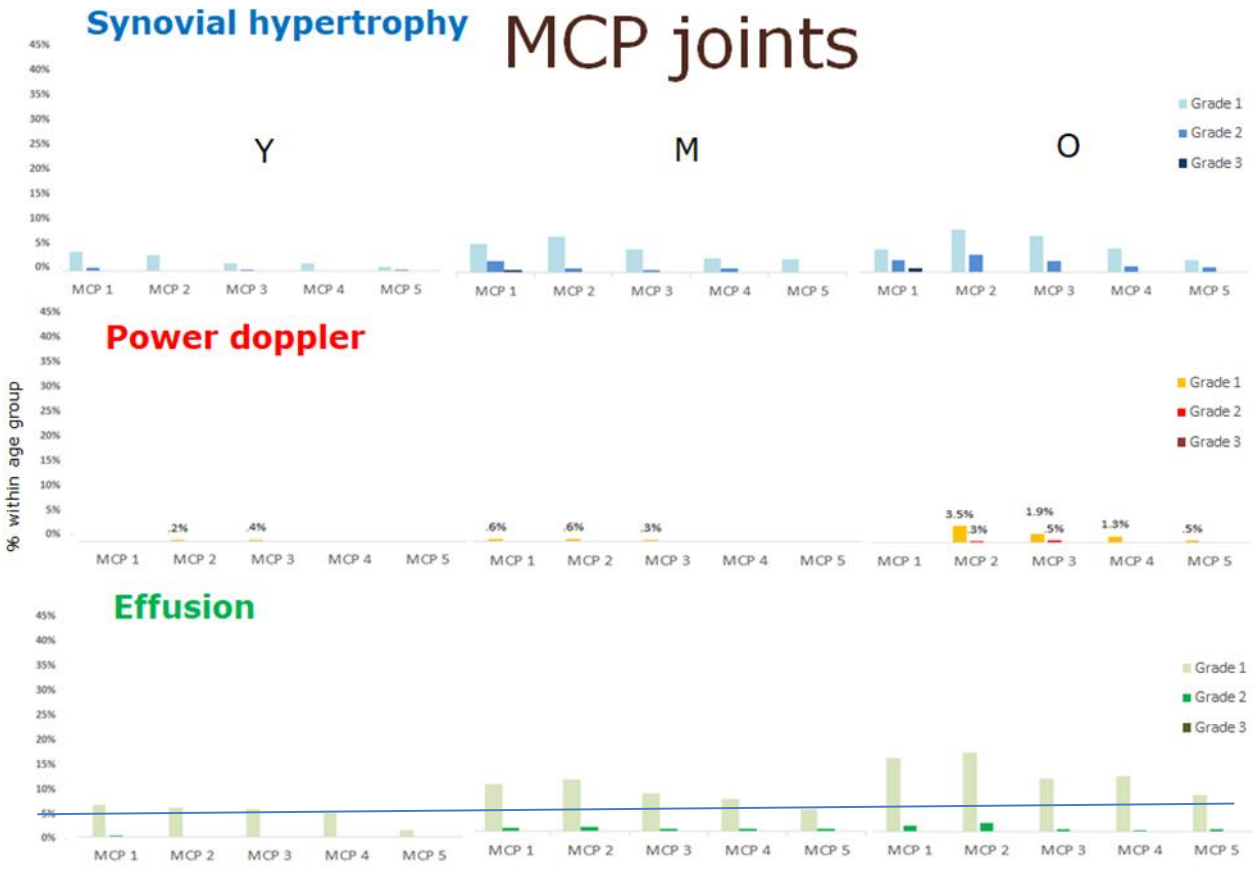

Figure 3-4 Column charts of percentage of grade ≥ 1 synovial hypertrophy, power Doppler and effusion in Healthy Subjects by age groups, in metacarpophalangeal joints 1-5

Y, young (age 18-39 years); M, middle (age 40-59 years); O, old (60-80 years)

3.3.4.2 Proximal interphalangeal joints

There were significantly higher proportions of HS O with SH grade ≥ 1 in PIP joints 1-5 ($p<0.001$ for PIPJ1-3; $p<0.05$ for PIPJ 4 and PIPJ 5) (Table 3-13). The HS O age group had the highest proportion of PD grade ≥1 in PIPJ 2 and PIPJ 3 ($p\leq0.05$).

	HS Y (18-39 years) grade ≥ 1	HS M (40-59 years) grade ≥ 1	HS O (60-80 years) grade ≥ 1	p value* HS Y vs M vs O G ≥1
SH				
PIPJ 1	5 (0.6)	31 (4.4)	17 (4.6)	<0.001
PIPJ 2	6 (0.7)	20 (2.8)	13 (3.5)	<0.001
PIPJ 3	9 (1.1)	19 (2.6)	18 (4.9)	<0.001
PIPJ 4	12 (1.5)	15 (2.1)	15 (4.0)	0.012
PIPJ 5	5 (0.6)	6 (0.8)	9 (2.4)	0.015
PD				
PIPJ 1	0 (0.0)	3 (0.4)	1 (0.3)	0.132
PIPJ 2	0 (0.0)	0 (0.0)	2 (0.5)	0.038
PIPJ 3	0 (0.0)	1 (0.1)	2 (0.5)	0.050
PIPJ 4	0 (0.0)	0 (0.0)	1 (0.3)	0.195
PIPJ 5	0 (0.0)	0 (0.0)	1 (0.3)	0.195
EF				
PIPJ 1	94 (11.6)	88 (12.6)	52 (14.2)	0.232
PIPJ 2	27 (3.3)	35 (4.8)	24 (6.5)	0.015
PIPJ 3	30 (3.7)	31 (4.3)	24 (6.4)	0.056
PIPJ 4	26 (3.2)	24 (3.3)	27 (7.3)	0.007
PIPJ 5	22 (2.7)	28 (3.8)	20 (5.4)	0.024

Table 3-13 Ultrasound findings grade ≥ 1 in proximal interphalangeal joints in healthy subjects according to age group

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); PIPJ, proximal interphalangeal joint; G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion; * Kendall's tau-b test

Synovial hypertrophy grade ≥ 1 was more prevalent in HS O in PIPJ 1-5 but the HS M age group had higher proportions of grade 1 SH compared to HS O. However, there were higher proportions of grade 2 SH in HS O compared to HS M (Table 3-14 and Figure 3-5), meaning older HS were more likely to have more severe grades of SH in the PIPJs. No grade 3 SH was seen in PIPJ 1-5 HS of any age group.

	HS Y (18-39 years)			HS M (40-59 years)			HS O (60-80 years)		
	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)
SH									
PIPJ 1	3 (0.4)	2 (0.2)	0 (0.0)	24 (3.4)	7 (1.0)	0 (0.0)	9 (2.5)	8 (2.2)	0 (0.0)
PIPJ 2	6 (0.7)	0 (0.0)	0 (0.0)	20 (2.8)	0 (0.0)	0 (0.0)	8 (2.2)	5 (1.3)	0 (0.0)
PIPJ 3	8 (1.0)	1 (0.1)	0 (0.0)	18 (2.5)	1 (0.1)	0 (0.0)	13 (3.5)	5 (1.3)	0 (0.0)
PIPJ 4	12 (1.5)	0 (0.0)	0 (0.0)	13 (1.8)	2 (0.3)	0 (0.0)	13 (3.5)	2 (0.5)	0 (0.0)
PIPJ 5	5 (0.6)	0 (0.0)	0 (0.0)	4 (0.6)	2 (0.3)	0 (0.0)	6 (1.6)	3 (0.8)	0 (0.0)
PD									
PIPJ 1	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
PIPJ 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
PIPJ 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
PIPJ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
PIPJ 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
EF									
PIPJ 1	83 (10.2)	11 (1.4)	0 (0.0)	72 (10.3)	16 (2.3)	0 (0.0)	45 (12.3)	7 (1.9)	0 (0.0)
PIPJ 2	26 (3.2)	1 (0.1)	0 (0.0)	32 (4.4)	3 (0.4)	0 (0.0)	24 (6.5)	0 (0.0)	0 (0.0)
PIPJ 3	29 (3.6)	1 (0.1)	0 (0.0)	28 (3.9)	3 (0.4)	0 (0.0)	22 (5.9)	2 (0.5)	0 (0.0)
PIPJ 4	26 (3.2)	0 (0.0)	0 (0.0)	23 (3.2)	1 (0.1)	0 (0.0)	24 (6.5)	2 (0.5)	1 (0.3)
PIPJ 5	21 (2.6)	1 (0.1)	0 (0.0)	25 (3.4)	2 (0.3)	1 (0.1)	18 (4.9)	2 (0.5)	0 (0.0)

Table 3-14 Ultrasound findings of synovial hypertrophy, power Doppler and effusion of grade 1 to 3 in proximal interphalangeal joints in healthy subjects according to age groups

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); PIP, proximal interphalangeal joint; G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion; * Fisher's exact test

HS O had significantly more grade ≥1 joint effusion in PIPJ 2, 4 and 5 ($p<0.05$). There was no significant difference in prevalence of grade ≥1 joint effusion in PIPJ 1 suggesting it is a common finding even in younger healthy subjects (see line demarking 5% prevalence of joint effusion in PIPJs in Figure 3-5). There were significantly more grade ≥1 EF in PIPJ 1 compared to each of the other PIPJs in all HS ($p <0.001$, McNemar's), and these were predominantly of grade 1 severity, with no HS within any age group having grade 3 EF in PIPJ 1 (Table 3-14).

The graphs in Figure 3-5 depict relatively lower abnormalities of SH, PD and EF in the PIP joints compared to the MCP joints. There were very low levels of PD detected across all age groups in the PIPJs; the highest grade detected was grade 2 in the PIPJs of two older individuals. This suggests PD grade ≥ 1 in the PIPJs is very rare in HS of any age.

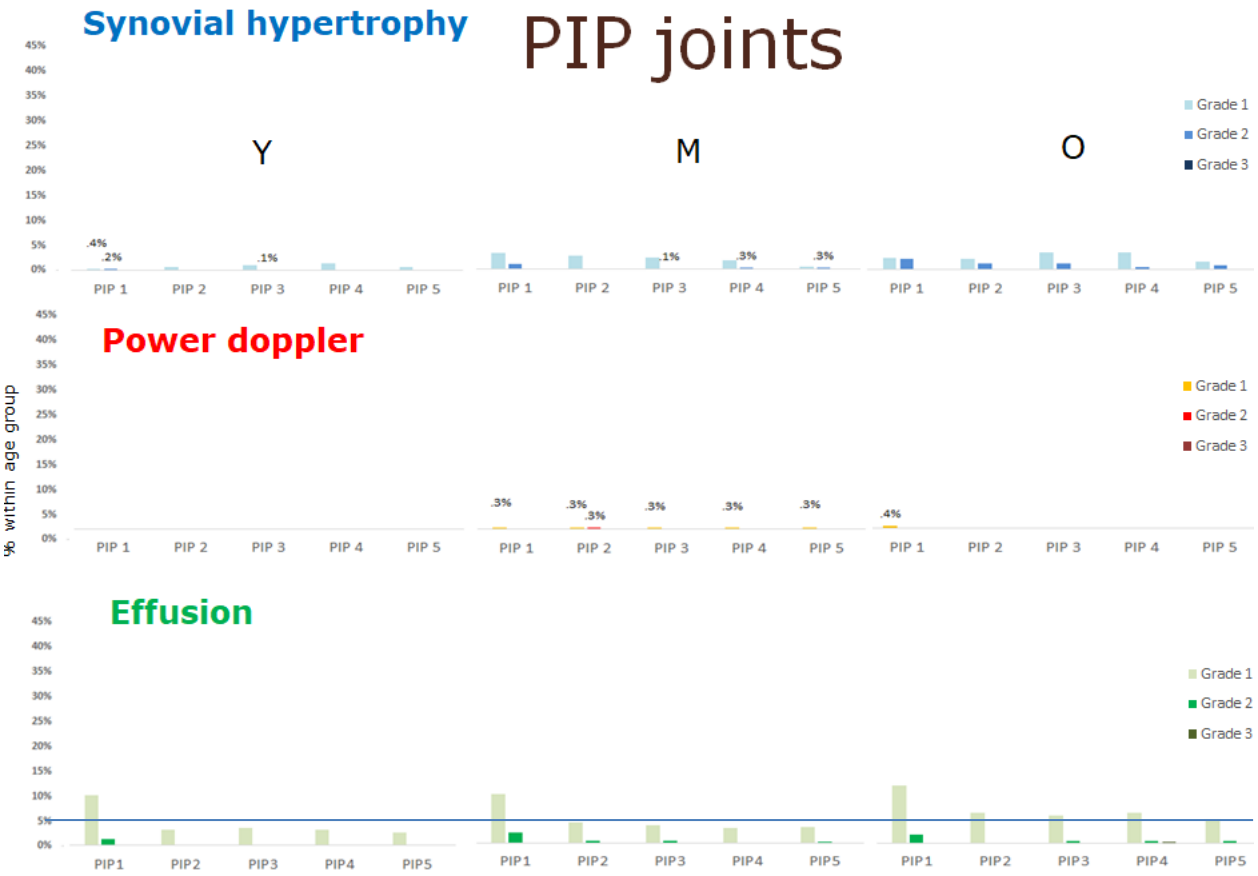

Figure 3-5 Column charts of percentage of grade 1-3 synovial hypertrophy, power Doppler and effusion in Healthy Subjects by age groups, in proximal interphalangeal joints 1-5

Y, young (age 18-39 years); M, middle (age 40-59 years); O, old (60-80 years)

3.3.4.3 Metatarsophalangeal joints

The prevalence of grade ≥1 SH and EF appeared to be much higher across the age range in the MTPJs compared to the MCPJs and PIPJs (Table 3-15 and Figure 3-6). There were significantly more grade ≥ 1 SH in MTPJ 1 in HS O.

	HS Y (18-39 years) grade ≥ 1	HS M (40-59 years) grade ≥ 1	HS O (60-80 years) grade ≥ 1	p value* HS Y vs M vs O G ≥1
SH				
MTPJ 1	288 (35.6)	290 (41.4)	194 (52.7)	<0.001
MTPJ 2	210 (25.9)	223 (31.9)	104 (28.3)	0.112
MTPJ 3	151 (18.6)	169 (24.1)	72 (19.6)	0.212
MTPJ 4	86 (10.6)	114 (16.3)	58 (15.8)	0.002
MTPJ 5	19 (2.3)	15 (2.1)	9 (2.4)	1.00
PD				
MTPJ 1	8 (1.0)	23 (3.3)	18 (4.9)	<0.001
MTPJ 2	1 (0.1)	1 (0.1)	6 (1.6)	0.003
MTPJ 3	3 (0.4)	2 (0.3)	1 (0.3)	0.746
MTPJ 4	3 (0.4)	2 (0.3)	3 (0.8)	0.482
MTPJ 5	1 (0.1)	0 (0.0)	0 (0.0)	0.627
EF				
MTPJ 1	449 (45.4)	322 (46.1)	253 (57.9)	0.475
MTPJ 2	316 (39.0)	255 (36.5)	134 (36.4)	0.288
MTPJ 3	200 (24.7)	201 (28.7)	114 (30.9)	0.015
MTPJ 4	153 (18.9)	148 (25.1)	89 (24.2)	0.040
MTPJ 5	49 (6.0)	52 (7.4)	18 (4.9)	0.840

Table 3-15 Ultrasound findings grade ≥ 1 in metatarsophalangeal joints in healthy subjects according to age group

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MTPJ, metatarsophalangeal joint; G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion; * Kendall's tau-b test

There were relatively low levels of power Doppler grade ≥ 1 in all MTP joints, but significantly more in MTPJ 1 and 2 in the HS O age group ($p<0.001$, $p<0.05$ respectively). Surprisingly there were two grade 3 PD in MTPJ 3 in HS in the youngest age group, and four grade 2 PD in MTPJs in this age group also. All but one of these grade 2 and 3 PD MTPJ 2-5 findings were from one 27 year old female HS who had never smoked, had a healthy BMI, had no past medical history, family history or personal history of psoriasis, no history of manual work or reported any physical activities. This represents an outlier of a HS with evidence of an asymptomatic and subclinical inflammatory arthritis in two MTPJs, which might be expected in a large study of over 900 subjects.

	HS Y (18-39 years)			HS M (40-59 years)			HS O (60-80 years)		
	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)
SH									
MTP 1	191 (23.6)	90 (11.1)	7 (0.9)	164 (23.4)	110 (15.7)	16 (2.3)	57 (15.5)	131 (35.6)	6 (1.6)
MTP 2	127 (15.7)	74 (9.1)	9 (1.1)	104 (14.9)	103 (14.7)	16 (2.3)	47 (12.8)	53 (14.4)	4 (1.1)
MTP 3	98 (12.1)	45 (5.6)	8 (1.0)	105 (15.0)	55 (7.9)	9 (1.3)	33 (9.0)	35 (9.5)	4 (1.1)
MTP 4	57 (7.0)	29 (3.6)	0 (0.0)	72 (10.3)	39 (5.6)	3 (0.4)	34 (9.2)	24 (6.5)	0 (0.0)
MTP 5	16 (2.0)	3 0.4)	0 (0.0)	12 (1.7)	3 (0.4)	0 (0.0)	8 (2.2)	1 (0.3)	0 (0.0)
PD									
MTP 1	7 (0.9)	1 (0.1)	0 (0.0)	19 (2.7)	4 (0.6)	0 (0.0)	14 (3.8)	4 (1.1)	0 (0.0)
MTP 2	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	4 (1.1)	2 (0.5)	0 (0.0)
MTP 3	1 (0.1)	0 (0.0)	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
MTP 4	1 (0.1)	2 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)
MTP 5	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
EF									
MTP1	320 (39.5)	112 (13.8)	17 (2.1)	209 (29.9)	97 (13.9)	16 (2.3)	167 (45.4)	38 (10.3)	8 (2.2)
MTP 2	269 (33.2)	47 (5.8)	0 (0.0)	184 (26.3)	58 (8.3)	13 (1.9)	91 (24.7)	39 (10.6)	4 (1.1)
MTP 3	178 (22.0)	21 (2.6)	1 (0.1)	148 (21.1)	42 (6.0)	11 (1.6)	84 (22.8)	24 (6.5)	6 (1.6)
MTP 4	135 (16.7)	18 (2.2)	0 (0.0)	113 (16.1)	28 (4.0)	7 (1.0)	59 (16.0)	26 (7.1)	4 (1.1)
MTP 5	48 (5.9)	1 (0.1)	0 (0.0)	46 (6.6)	5 (0.7)	1 (0.1)	18 (4.9)	0 (0.0)	0 (0.0)

Table 3-16 Ultrasound findings of synovial hypertrophy, power Doppler and effusion of grade 1 to 3 in metatarsophalangeal joints in healthy subjects according to age groups

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MTP, metatarsophalangeal joint; G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion; * Fisher's exact test

There were not many differences in prevalence of grade ≥1 EF across the age groups, with only low level significant differences in MTPJ 3 and 4 ($p<0.05$) (Table 3-15). This may reflect that grade ≥ 1 EF in MTPJs 1-5 is common across the age range in healthy subjects.

MTPJ 1 had most ultrasound detected abnormalities (Figure 3-6) which is expected as this joint is subject to high mechanical loading forces. There were significantly more grade ≥1 SH, PD and EF in MTP 1 in HS in all age groups compared to MTP2-5 ($p<0.001$, McNemar's).

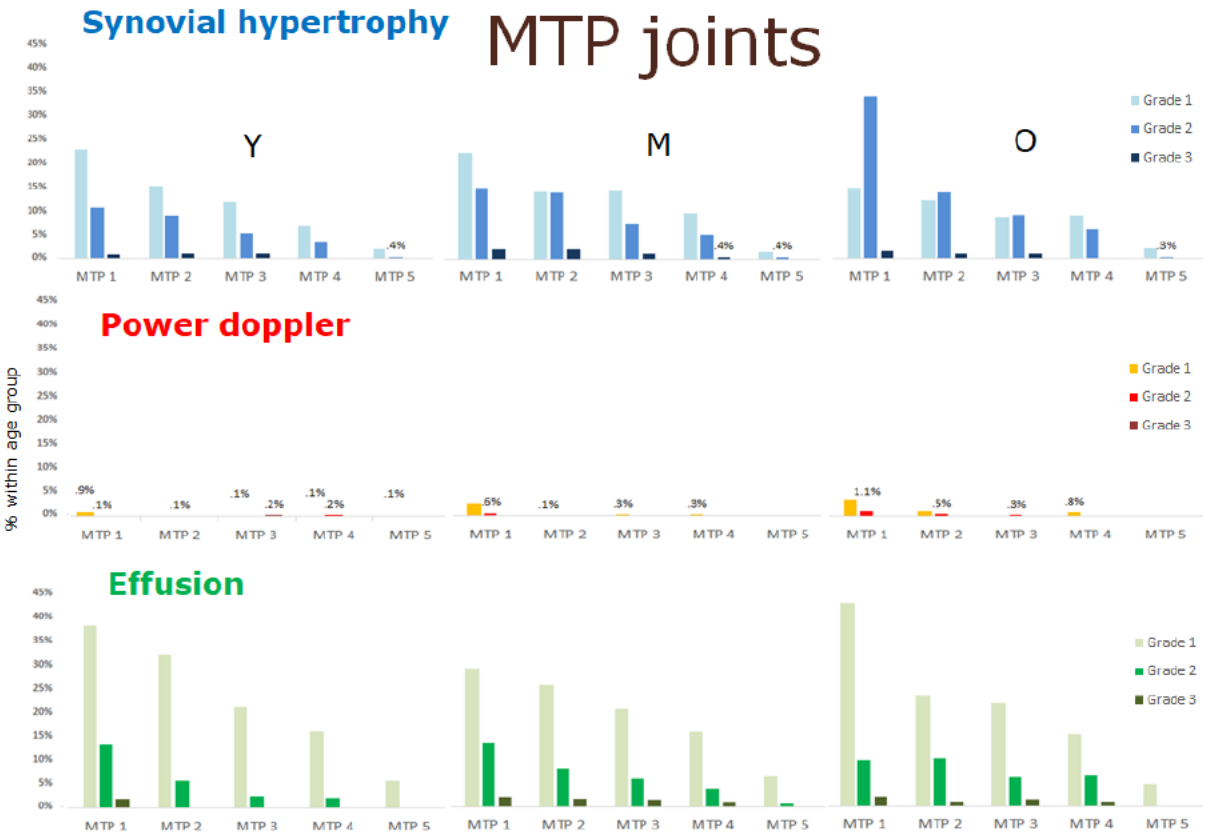

Figure 3-6 Column charts of percentage of grade 1-3 synovial hypertrophy, power Doppler and effusion in Healthy Subjects by age groups, in metatarsophalangeal joints 1-5

Y, young (age 18-39 years); M, middle (age 40-59 years); O, old (60-80 years)

3.3.4.4 Wrists

The proportions of grade ≥1 SH and EF in wrists were higher than those seen in the MCPJs and PIPJs (Table 3-17 and Figure 3-7). There were significantly higher proportions of grade ≥ 1 SH and PD but not EF in the HS O age group (p<0.001).

	HS Y (18-39 years) grade ≥ 1	HS M (40-59 years) grade ≥ 1	HS O (60-80 years) grade ≥ 1	p value* HS Y vs M vs O G ≥1
SH	92 (11.4)	123 (17.6)	90 (24.9)	<0.001
PD	7 (0.9)	18 (2.6)	17 (4.7)	<0.001
EF	117 (14.5)	97 (13.8)	45 (12.5)	0.393

Table 3-17 Ultrasound findings grade ≥ 1 in wrist joints in healthy subjects according to age group

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion; * Kendall's tau-b test

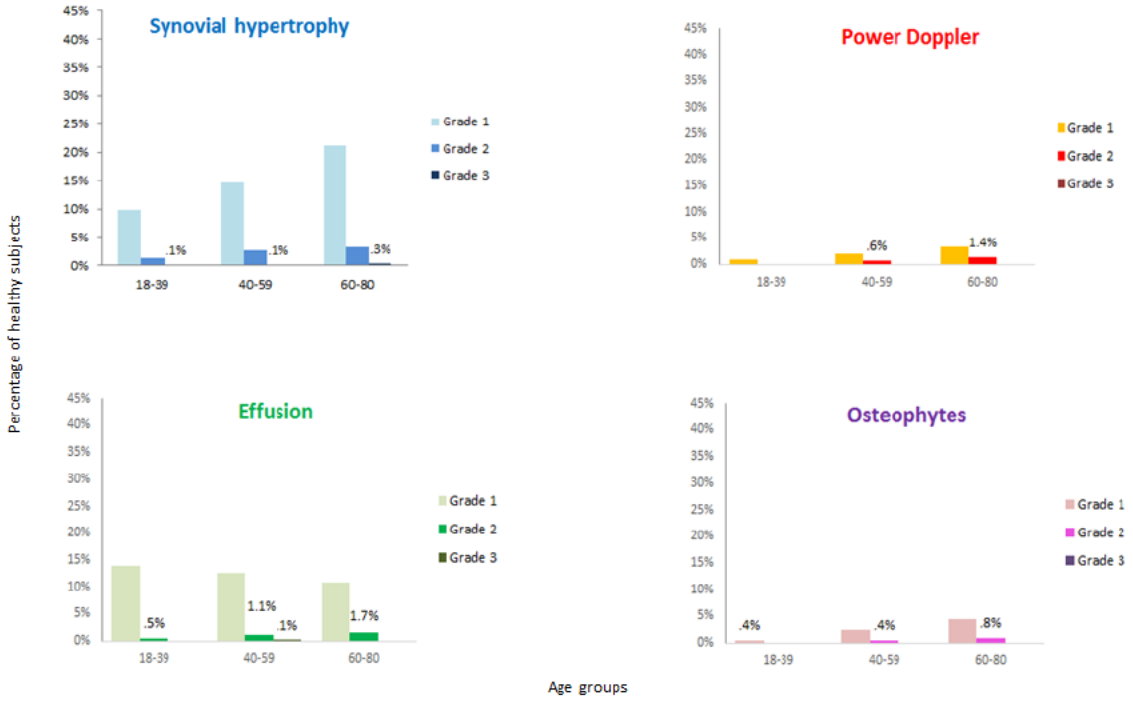

Figure 3-7 Column charts of percentage of grade 1-3 synovial hypertrophy, power Doppler and effusion in Healthy Subjects by age groups, in wrist joints

Y, young (age 18-39 years); M, middle (age 40-59 years); O, old (60-80 years)

The severity of SH was mostly grade 1, but there was one HS with grade 3 SH recorded in each of the age groups (Table 3-18). Power Doppler was low across the age groups, and there were no grade 2 seen in the youngest age group, and grade 3 PD in the wrist was not seen in HS in any age group.

	HS Y (18-39 years)			HS M (40-59 years)			HS O (60-80 years)		
	G 1 n (%)	**G 2 n (%)**	**G 3 n (%)**	**G 1 n (%)**	**G 2 n (%)**	**G 3 n (%)**	**G 1 n (%)**	**G 2 n (%)**	**G 3 n (%)**
SH	80 (9.9)	11 (1.4)	1 (0.1)	103 (14.7)	19 (2.7)	1 (0.1)	77 (21.3)	12 (3.3)	1 (0.3)
PD	7 (0.9)	0 (0.0)	0 (0.0)	14 (2.0)	4 (0.6)	0 (0.0)	12 (3.3)	5 (1.4)	0 (0.0)
EF	113 (14.0)	4 (0.5)	0 (0.0)	88 (12.6)	8 (1.1)	1 (0.1)	39 (10.8)	6 (1.7)	0 (0.0)

Table 3-18 Ultrasound findings of synovial hypertrophy, power Doppler and effusion of grade 1 to 3 in wrist joints in healthy subjects according to age groups

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); G, grade; SH, synovial hypertrophy; PD, Power Doppler, EF, Effusion; * Fisher's exact test

3.3.5 Occupational status

A large proportion of healthy subjects included in this study worked in occupations related to hospital settings making recruitment easy. There were 44.5% citing doctor, nurse or allied health care professions (such as physiotherapist or pharmacist) as their occupation or previous occupation if retired (Table 3-19).

Occupation	Number (%)
Doctor	198 (20.8)
Nurse	176 (18.4)
Student	95 (10.0)
Admin/Office work	93 (9.7)
Manual worker	75 (7.9)
Secretary	60 (6.3)
Allied health care professional	51 (5.3)
Scientist	49 (5.1)
Teacher	36 (3.8)
Housewife	29 (3.0)
Retail	20 (2.1)
None	12 (1.3)
Manager	12 (1.3)
Academic	10 (1.0)
Other	9 (0.9)
Retired (no further information)	5 (0.5)

Table 3-19 current or previous main occupations of healthy subjects

3.3.5.1 Occupational status and synovial hypertrophy

There were 75 (7.9%) healthy subjects currently, previously or retired from working in manual occupations. There were significantly more grade ≥1 SH in current/previous manual workers compared to non-manual workers in MCPJ 2-4 ($p<0.001$), PIPJ 1 and MTPJ 5 ($p<0.05$) (Table 3-20). These differences may be due to more mechanical load through these joints in manual occupations.

	Manual occupation	Non manual occupation	p value*
	number of joints grade ≥ 1, n (%)	number of joints grade ≥ 1, n (%)	Manual vs non manual
MCPJ 1 SH	17 (11.3)	117 (6.7)	0.117
MCPJ 2 SH	24 (16.0)	114 (6.5)	<0.001
MCPJ 3 SH	24 (16.0)	68 (3.9)	<0.001
MCPJ 4 SH	15 (10.0)	51 (2.9)	<0.001
MCPJ 5 SH	10 (6.7)	35 (2.0)	0.006
PIPJ 1 SH	10 (7.1)	43 (2.5)	0.019
PIPJ 2 SH	4 (2.7)	35 (2.0)	0.597
PIPJ 3 SH	5 (3.3)	41 (2.3)	0.486
PIPJ 4 SH	6 (4.0)	36 (2.1)	0.246
PIPJ 5 SH	1 (0.7)	19 (1.1)	1
WRIST SH	25 (18.4)	279 (16.1)	0.661
MTPJ 1 SH	65 (46.4)	706 (40.8)	0.214
MTPJ 2 SH	50 (35.7)	486 (28.1)	0.136
MTPJ 3 SH	37 (26.4)	355 (20.5)	0.127
MTPJ 4 SH	24 (17.1)	234 (13.5)	0.395
MTPJ 5 SH	8 (5.7)	35 (2.0)	0.033

Table 3-20 synovial hypertrophy grade ≥ 1 in joints in manual workers vs non manual workers

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joints; MTPJ, metatarsophalangeal joint; SH, synovial hypertrophy; *Fisher's exact test

3.3.5.2 Occupational status and Power Doppler

There were significantly more grade ≥1 PD in the manual occupation group in MCPJ 2 ($p<0.05$) (Table 3-21). This may be explained by MCPJ 2 having more mechanical load through the joint in manual workers.

	Manual occupation	Non manual occupation	p value*
	number of joints grade ≥ 1, n (%)	number of joints grade ≥ 1, n (%)	Manual vs non manual
MCPJ 1 PD	0 (0)	4 (0.2)	1
MCPJ 2 PD	3 (2.0)	16 (0.9)	0.016
MCPJ 3 PD	3 (2.0)	11 (0.6)	0.131
MCPJ 4 PD	1 (0.7)	4 (0.2)	0.348
MCPJ 5 PD	1 (0.7)	1 (0.1)	0.157
PIPJ 1 PD	0 (0)	4 (0.2)	1
PIPJ 2 PD	0 (0)	2 (0.1)	1
PIPJ 3 PD	0 (0.0)	3 (0.2)	1
PIPJ 4 PD	0 (0.0)	1 (0.1)	n/a
PIPJ 5 PD	0 (0)	1 (0.1)	n/a
WRIST PD	4 (2.9)	37 (2.1)	0.097
MTPJ 1 PD	2 (1.4)	47 (2.7)	0.641
MTPJ 2 PD	0 (0)	8 (0.5)	0.661
MTPJ 3 PD	1 (0.7)	5 (0.3)	0.385
MTPJ 4 PD	0 (0)	8 (0.5)	1
MTPJ 5 PD	0 (0)	1 (0.1)	n/a

Table 3-21 power Doppler grade ≥ 1 in joints in manual workers vs non manual workers

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joints; MTPJ, metatarsophalangeal joint; PD, power Doppler; *Fisher's exact test

3.3.5.3 Occupational status and joint effusion

The comparison of proportion of grade ≥1 joint effusion between manual and non-manual workers did not follow the same pattern of more grade ≥1 abnormalities in load bearing joints as seen with SH and PD. There were low level significant differences in MCPJ 3 and 4 ($p<0.05$) with EF more common in the manual occupation group (Table 3-22). However, there were also low level significant differences in PIPJ 2, MTPJ 1 and MTPJ 2 but with grade ≥ 1 EF more common in the non-manual worker group ($p<0.05$). This difference may be due to other confounding factors such as age, because the manual worker group was older than the non-manual worker group: median age 58 years (IQR 43, 66) versus 42 years (IQR 30, 56).

	Manual occupation	Non manual occupation	p value
	number of joints grade ≥ 1, n (%)	number of joints grade ≥ 1, n (%)	Manual vs non manual
MCPJ 1 EF	12 (8.0)	183 (10.5)	0.647
MCPJ 2 EF	19 (12.7)	184 (10.5)	0.62
MCPJ 3 EF	20 (13.3)	132 (7.5)	0.045
MCPJ 4 EF	19 (12.7)	121 (6.9)	0.04
MCPJ 5 EF	11 (7.3)	70 (4.0)	0.127
PIPJ 1 EF	18 (12.9)	216 (12.5)	0.953
PIPJ 2 EF	2 (1.3)	83 (4.7)	0.049
PIPJ 3 EF	6 (4.0)	78 (4.5)	0.312
PIPJ 4 EF	8 (5.3)	69 (3.9)	0.521
PIPJ 5 EF	5 (3.3)	65 (3.7)	1
WRIST EF	15 (11.0)	243 (14.0)	0.465
MTPJ 1 EF	56 (40.0)	925 (53.4)	0.006
MTPJ 2 EF	39 (27.9)	663 (38.3)	0.027
MTPJ 3 EF	32 (22.9)	481 (27.8)	0.448
MTPJ 4 EF	21 (15.0)	367 (21.2)	0.11
MTPJ 5 EF	8 (5.7)	111 (6.4)	0.904

Table 3-22 effusion grade ≥ 1 in joints in manual workers vs non manual workers

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joints; MTPJ, metatarsophalangeal joint; EF, effusion; *Fisher's exact test

3.3.5.4 Occupational status and osteophytes

There were significantly more osteophytes grade ≥ 1 in the manual occupation group in MCPJ 3 and 5, PIPJ 1 and 3-5 ($p<0.001$) (Table 3-23), and also to lesser degree of significance in MCPJ 1, 2 and 4, and MTPJ 5 ($p<0.05$). This may be due to the HS in the manual worker group being older.

	Manual job	Non manual job	p value
	number of joints grade ≥ 1, n (%)	number of joints grade ≥ 1, n (%)	Manual vs non manual
MCPJ 1 Os	27 (18.8)	157 (9.3)	0.002
MCPJ 2 Os	35 (24.3)	254 (15.0)	0.014
MCPJ 3 Os	29 (20.1)	119 (7.0)	<0.001
MCPJ 4 Os	12 (8.3)	62 (3.7)	0.039
MCPJ 5 Os	19 (13.2)	77 (4.5)	<0.001
PIPJ 1 Os	30 (22.4)	163 (9.7)	<0.001
PIPJ 2 Os	25 (17.4)	188 (11.1)	0.057
PIPJ 3 Os	27 (18.8)	173 (10.2)	<0.001
PIPJ 4 Os	30 (20.8)	146 (8.6)	<0.001
PIPJ 5 Os	25 (17.4)	152 (9.0)	0.001
WRIST Os	4 (3.1)	37 (2.2)	0.593
MTPJ 1 Os	27 (20.1)	236 (14.1)	0.12
MTPJ 2 Os	16 (11.9)	113 (6.7)	0.107
MTPJ 3 Os	10 (7.5)	56 (3.3)	0.064
MTPJ 4 Os	10 (7.5)	59 (3.5)	0.074
MTPJ 5 Os	21 (15.7)	119 (7.1)	0.003

Table 3-23 osteophytes grade ≥ 1 in joints in manual workers vs non manual workers

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joints; MTPJ, metatarsophalangeal joint; Os, osteophyte; *Fisher's exact test

3.3.6 Physical hobbies

The present and previous major physical hobbies of healthy subjects were collected. They were then grouped into hobbies which involved high or low impact on upper limbs or lower limb, examples of which are in Table 3-24.

High impact upper limb hobbies	High impact lower limb hobbies
Weight lifting	Running
Boxing	Aerobics
Martial arts	Skiing
Tennis	Football

Table 3-24 examples of high impact upper limb and lower limb hobbies

3.3.6.1 Synovial hypertrophy and hobbies with high impact on upper limbs

The group of HS not practicing hobbies with high impact on upper limbs had higher proportions of grade ≥1 SH in all MCPJs, PIPJs and wrist joints except PIPJ 5, but this was only significant

in MCPJ 3 ($p<0.05$) (Table 3-25). This may be because this group was older: median age 45 years (IQR 32, 58), compared to those HS who participated in hobbies involving high impact on upper limb joints with median age 33 years (IQR 26, 47).

	HS practising upper limb high impact hobbies	**HS not practising upper limb high impact hobbies**	**p value***
	grade ≥ 1, n (%)	grade ≥ 1, n (%)	
MCPJ 1 SH	22 (5.9)	112 (7.3)	0.528
MCPJ 2 SH	21 (5.6)	117 (7.7)	0.105
MCPJ 3 SH	8 (2.1)	84 (5.5)	0.003
MCPJ 4 SH	10 (2.7)	56 (3.7)	0.085
MCPJ 5 SH	8 (2.1)	37 (2.4)	0.865
PIPJ 1 SH	5 (1.3)	48 (3.2)	0.157
PIPJ 2 SH	6 (1.6)	33 (2.2)	0.709
PIPJ 3 SH	4 (1.1)	42 (2.8)	0.148
PIPJ 4 SH	7 (1.9)	35 (2.3)	0.725
PIPJ 5 SH	5 (1.3)	15 (1.0)	0.589
WRIST SH	53 (14.2)	251 (16.8)	0.308

Table 3-25 synovial hypertrophy grade ≥ 1 in healthy subjects practicing hobbies with high impact on upper limbs

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joints; HS, healthy subjects; SH, synovial hypertrophy; *Fisher's exact test

3.3.6.2 Power Doppler and hobbies with high impact on upper limbs

The healthy subjects who did not practice hobbies with high impact on the upper limbs had higher proportions of PD grade ≥1 in MCPJs, PIPJs, and wrists joints but this was only statistically significant in MCPJ 2 and the wrist joints ($p=0.05$) (Table 3-26), which may be because this group was older.

	HS practising upper limb high impact hobbies	HS not practising upper limb high impact hobbies	p value*
	grade ≥ 1, n (%)	grade ≥ 1, n (%)	
MCPJ 1 PD	0 (0.0)	4 (0.3)	1
MCPJ 2 PD	1 (0.3)	18 (1.2)	0.009
MCPJ 3 PD	2 (0.5)	12 (0.8)	1
MCPJ 4 PD	1 (0.3)	4 (0.3)	1
MCPJ 5 PD	0 (0.0)	2 (0.1)	1
PIPJ 1 PD	0 (0.0)	4 (0.3)	0.593
PIPJ 2 PD	0 (0.0)	2 (0.1)	1
PIPJ 3 PD	0 (0.0)	3 (0.2)	1
PIPJ 4 PD	0 (0.0)	1 (0.1)	1
PIPJ 5 PD	0 (0.0)	1 (0.1)	1
WRIST PD	3 (0.8)	38 (2.5)	0.009

Table 3-26 Power Doppler grade ≥ 1 in healthy subjects practicing hobbies with high impact on upper limbs

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joints; HS, healthy subjects; PD, Power Doppler; *Fisher's exact test

3.3.6.3 Joint effusion and hobbies with high impact on upper limbs

There were no statistically significant differences in the proportion of joint effusion grade ≥1 in the MCPJs, PIPJs, and wrist joints between HS who did and did not practice hobbies with high impact on upper limbs (Table 3-27).

	HS practising upper limb high impact hobbies	HS not practising upper limb high impact hobbies	p value*
	grade ≥ 1, n (%)	grade ≥ 1, n (%)	
MCPJ 1 EF	32 (8.5)	163 (10.7)	0.516
MCPJ 2 EF	36 (9.6)	167 (10.9)	0.69
MCPJ 3 EF	28 (7.4)	124 (8.1)	0.821
MCPJ 4 EF	30 (8.0)	110 (7.2)	0.693
MCPJ 5 EF	12 (3.2)	69 (4.5)	0.427
PIPJ 1 EF	58 (15.4)	176 (11.8)	0.156
PIPJ 2 EF	18 (4.8)	67 (4.4)	0.192
PIPJ 3 EF	18 (4.8)	67 (4.4)	0.817
PIPJ 4 EF	18 (4.8)	59 (3.9)	0.546
PIPJ 5 EF	18 (4.8)	52 (3.4)	0.329
WRIST EF	48 (12.8)	210 (14.1)	0.465

Table 3-27 Joint effusion grade ≥ 1 in healthy subjects practicing hobbies with high impact on upper limbs

MCPJ, metacarpophalangeal joint; PIPJ, proximal interphalangeal joints; HS, healthy subjects; EF, effusion; *Fisher's exact test

3.3.6.4 Synovial hypertrophy and hobbies with high impact on lower limbs

There were no significant differences in proportion of grade ≥ 1 SH in the MTP joints of healthy subjects who did and did not practice hobbies which involve high impact on the lower limb joints (Table 3-28). The median age of HS not reporting hobbies with a high impact on the lower limb joints was 47 years (IQR 32, 58) compared to 36 (IQR 28, 39).

	HS practising lower limb high impact hobbies	HS not practising lower limb high impact hobbies	p value*
	grade ≥ 1, n (%)	grade ≥ 1, n (%)	
MTPJ 1 SH	274 (43.9)	497 (39.8)	0.164
MTPJ 2 SH	187 (30.0)	349 (27.9)	0.732
MTPJ 3 SH	129 (20.7)	263 (21.0)	0.827
MTPJ 4 SH	76 (12.2)	182 (14.6)	0.304
MTPJ 5 SH	13 (2.1)	30 (2.4)	0.768

Table 3-28 Synovial hypertrophy grade ≥ 1 in healthy subjects practicing hobbies with high impact on lower limbs

MTPJ, metatarsophalangeal joint; HS, healthy subjects; SH, synovial hypertrophy; *Fisher's exact test

3.3.6.5 Power Doppler and hobbies with high impact on lower limbs

There were no significant differences in proportion of grade ≥ 1 PD in the MTP joints of healthy subjects who did and did not practice hobbies which involve high impact on the lower limbs (Table 3-29).

	HS practising lower limb high impact hobbies	HS not practising lower limb high impact hobbies	p value*
	grade ≥ 1, n (%)	grade ≥ 1, n (%)	
MTPJ 1 PD	18 (2.9)	31 (2.5)	0.681
MTPJ 2 PD	2 (0.3)	6 (0.5)	1
MTPJ 3 PD	1 (0.2)	5 (0.4)	0.674
MTPJ 4 PD	0 (0)	8 (0.6)	0.074
MTPJ 5 PD	1 (0.2)	0 (0)	0.334

Table 3-29 Power Doppler grade ≥ 1 in healthy subjects practicing hobbies with high impact on lower limbs

MTPJ, metatarsophalangeal joint; HS, healthy subjects; PD, power Doppler; *Fisher's exact test

3.3.6.6 Joint effusion and hobbies with high impact on lower limbs

Healthy subjects who practiced hobbies which involve high impact on the lower limb joints had more grade ≥1 EF in MTPJ 1 ($p<0.05$) (Table 3-30). This may reflect hobbies which put high mechanical loads through the feet resulting in more joint effusion in MTPJ 1.

	HS practising lower limb high impact hobbies	HS not practising lower limb high impact hobbies	p value*
	grade ≥ 1, n (%)	grade ≥ 1, n (%)	
MTPJ 1 EF	351 (56.3)	632 (50.6)	0.026
MTPJ 2 EF	246 (39.4)	458 (36.6)	0.488
MTPJ 3 EF	182 (29.2)	332 (26.6)	0.431
MTPJ 4 EF	127 (20.4)	262 (21.0)	0.921
MTPJ 5 EF	34 (5.4)	85 (6.8)	0.439

Table 3-30 Joint effusion grade ≥ 1 in healthy subjects practicing hobbies with high impact on lower limbs

MTPJ, metatarsophalangeal joint; HS, healthy subjects; EF, effusion; *Fisher's exact test

3.3.7 Osteophytes

There were significantly more grade ≥1 osteophytes (Os) in the older age groups in MCP 1-3 ($p<0.001$) and MCPJ 4 ($p<0.05$). The highest proportions of grade ≥1 Os were not in the oldest age group (HS O) for all joints, but were highest in the middle age group (HS M) for: MCPJ 3-5, wrists, MTPJ 2 and 3 (indicated in red in Table 3-31). This may be because HS with evidence of hand osteoarthritis (according to ACR criteria) were excluded from this study, so ultrasound has detected osteophytes in the HS M group before they had become clinically evident.

	HS Y (18-39 years) Grade ≥ 1, n (%)	HS M (40-59 years) Grade ≥ 1 n (%)	HS O (60-80 years) Grade ≥ 1 n (%)	p value* HS Y vs M vs O Grade ≥1
MCPJ 1 Os	37 (3.7)	85 (12.1)	73 (20.2)	<0.001
MCPJ 2 Os	63 (8.1)	148 (21.0)	78 (21.6)	<0.001
MCPJ 3 Os	29 (3.7)	82 (11.6)	37 (10.2)	<0.001
MCPJ 4 Os	17 (2.2)	40 (5.7)	17 (4.7)	0.004
MCPJ 5 Os	28 (3.6)	50 (7.1)	18 (5.0)	0.062
PIPJ 1 Os	18 (2.3)	81 (11.9)	94 (26.2)	<0.001
PIPJ 2 Os	40 (5.1)	112 (15.9)	62 (17.1)	<0.001
PIPJ 3 Os	33 (4.2)	110 (15.6)	60 (16.5)	<0.001
PIPJ 4 Os	36 (4.7)	92 (13.1)	50 (13.7)	<0.001
PIPJ 5 Os	43 (5.5)	76 (10.9)	59 (16.3)	<0.001
Wrist Os	3 (0.4)	19 (2.8)	41 (2.2)	<0.001
MTPJ 1 Os	18 (2.3)	93 (15.3)	142 (39.5)	<0.001
MTPJ 2 Os	31 (4.0)	66 (9.7)	32 (9.0)	<0.001
MTPJ 3 Os	14 (1.8)	35 (5.1)	17 (4.7)	0.001
MTPJ 4 Os	14 (1.8)	36 (5.3)	19 (5.3)	<0.001
MTPJ 5 Os	40 (5.1)	62 (9.1)	38 (10.5)	<0.001

Table 3-31 Ultrasound findings of osteophytes grade≥ 1 in metacarpophalangeal, proximal interphalangeal, metatarsophalangeal and wrist joints in healthy subjects according to age group

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; Os, osteophyte. * Kendall's tau-b test

Further examination of the grade ≥1 Os in the HS M and HS O groups revealed higher proportions of grade 2 and/or sometimes grade 3 Os, in the joints in which the middle age group had higher proportions of grade 1 Os (indicated in red in Table 3-32). Therefore the HS O group

often had more severe grades of Os even if they did not have the highest proportion of grade ≥1 Os in every joint scanned.

	HS Y (18-39 years)			HS M (40-59 years)			HS O (60-80 years)		
	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)	G 1 n (%)	G 2 n (%)	G 3 n (%)
MCPJ 1 Os	26 (3.3)	1 (0.1)	0 (0.0)	75 (10.7)	9 (1.3)	1 (0.1)	50 (13.8)	21 (5.8)	2 (0.6)
MCPJ 2 Os	61 (7.8)	2 (0.3)	0 (0.0)	136 (19.3)	11 (1.6)	1 (0.1)	59 (16.3)	18 (5.0)	1 (0.3)
MCPJ 3 Os	29 (3.7)	0 (0.0)	0 (0.0)	79 (11.2)	3 (0.4)	0 (0.0)	32 (8.8)	5 (1.4)	0 (0.0)
MCPJ 4 Os	17 (2.2)	0 (0.0)	0 (0.0)	38 (5.4)	2 (0.3)	0 (0.0)	14 (3.9)	3 (0.8)	0 (0.0)
MCPJ 5 Os	28 (3.6)	0 (0.0)	0 (0.0)	42 (6.0)	8 (1.1)	0 (0.0)	15 (4.1)	2 (0.6)	1 (0.3)
PIPJ 1 Os	18 (2.3)	0 (0.0)	0 (0.0)	66 (9.7)	14 (2.1)	1 (0.1)	62 (17.3)	27 (7.5)	5 (1.4)
PIPJ 2 Os	39 (5.0)	1 (0.1)	0 (0.0)	105 (14.9)	7 (1.0)	0 (0.0)	45 (12.4)	16 (4.4)	1 (0.3)
PIPJ 3 Os	33 (4.2)	0 (0.0)	0 (0.0)	102 (14.5)	7 (1.0)	1 (0.1)	39 (10.7)	20 (5.5)	1 (0.3)
PIPJ 4 Os	34 (4.4)	2 (0.3)	0 (0.0)	87 (12.4)	4 (0.6)	1 (0.1)	39 (10.7)	11 (3.0)	0 (0.0)
PIPJ 5 Os	43 (5.5)	0 (0.0)	0 (0.0)	69 (9.8)	8 (1.1)	0 (0.0)	49 (13.5)	9 (2.5)	1 (0.3)
Wrist Os	3 (0.4)	0 (0.0)	0 (0.0)	16 (2.4)	3 (0.4)	0 (0.0)	35 (1.9)	6 (0.3)	0 (0.0)
MTPJ 1 Os	17 (2.2)	1 (0.1)	0 (0.0)	58 (8.6)	27 (4.0)	18 (2.7)	60 (16.7)	47 (13.1)	35 (9.7)
MTPJ 2 Os	29 (3.7)	2 (0.3)	0 (0.0)	47 (6.9)	19 (2.8)	0 (0.0)	24 (6.7)	6 (1.7)	2 (0.6)
MTPJ 3 Os	14 (1.8)	0 (0.0)	0 (0.0)	28 (4.1)	7 (1.0)	0 (0.0)	10 (2.8)	7 (1.9)	0 (0.0)
MTPJ 4 Os	14 (1.8)	0 (0.0)	0 (0.0)	32 (4.7)	4 (0.6)	0 (0.0)	13 (3.6)	5 (1.4)	1 (0.3)
MTPJ 5 Os	40 (5.1)	0 (0.0)	0 (0.0)	51 (7.5)	11 (1.6)	0 (0.0)	30 (8.3)	7 (1.9)	1 (0.3)

Table 3-32 Ultrasound findings of osteophytes of grade 1 to 3 in metacarpophalangeal, proximal interphalangeal, wrist and metatarsophalangeal joints in healthy subjects according to age group

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subject (60-80 years old); MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; G, grade; Os, osteophyte

The graphs in Figure 3-8 show that grade 1 osteophytes were common in the general population in asymptomatic individuals. The line demarcating 5% shows that all in MCPJs, PIPJs and MTPJs at least 5% of the healthy subjects in the HS M and HS O age groups had at least grade

1 osteophytes. Even the youngest age group had at least 5% of HS with grade 1 osteophytes in MCPJ 2, PIPJ 2 and 5 and MTPJ 5.

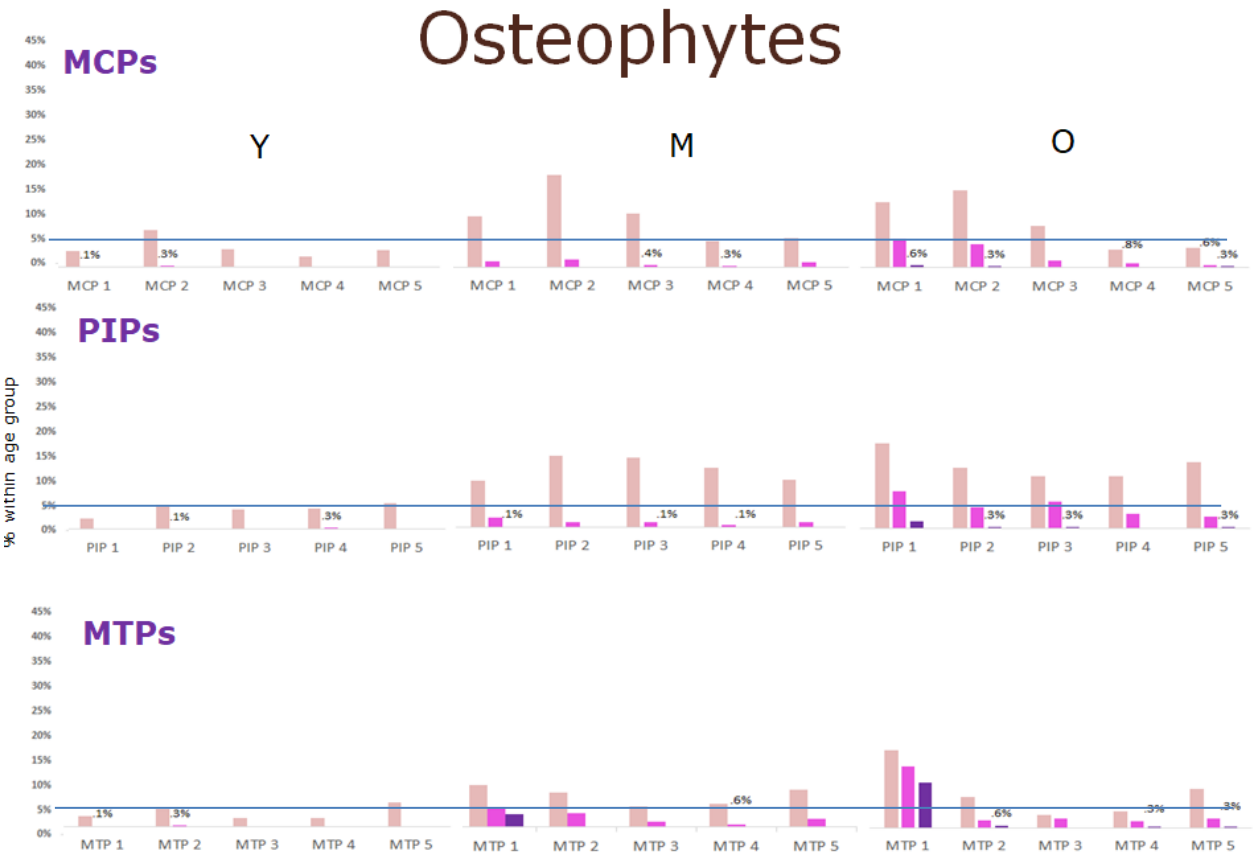

Figure 3-8 Column charts of percentage of grade 1-3 osteophytes in Healthy Subjects by age groups, in metacarpophalangeal joints (MCP) 1-5, proximal interphalangeal joints (PIP) 1-5 and metatarsophalangeal joints (MTP) 1-5

Y, young (age 18-39 years); M, middle (age 40-59 years); O, old (60-80 years)

Prevalence of grade ≥ 1 osteophytes appears to increase between the ages of 30-39 years and 40-49 years (Table 33-3). There were significant differences in grade ≥ 1 Os between these two age decades in: MCPJ 2, PIPJ 3, wrist and MTPJ 1, ($p<0.01$), and to a lesser degree of significance in: MCPJ 1, PIPJ 1, 2, 4 and MTPJ 5 ($p<0.05$).

	Age deciles in years, n (%)					
Os G ≥ 1	**18-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-80**
MCPJ 1	11 (2.7)	16 (4.3)	34 (9.7)	51 (14.4)	32 (14.4)	41 (29.5)
MCPJ 2	30 (7.3)	33 (8.9)	71 (20.3)	77 (21.8)	44 (19.6)	34 (24.5)
MCPJ 3	8 (2.0)	21 (5.7)	31 (8.9)	51 (14.4)	18 (8.0)	19 (13.7)
MCPJ 4	4 (1.0)	13 (3.5)	18 (5.1)	22 (6.2)	10 (4.5)	7 (5.0)
MCPJ 5	10 (2.4)	18 (4.9)	22 (6.3)	28 (7.9)	10 (4.5)	8 (5.8)
PIPJ 1	7 (1.7)	11 (3.0)	23 (6.8)	58 (17.0)	53 (24.1)	41 (29.5)
PIPJ 2	19 (4.6)	21 (5.7)	40 (11.4)	72 (20.3)	36 (16.1)	26 (18.7)
PIPJ 3	16 (3.9)	17 (4.6)	43 (12.3)	67 (18.9)	37 (16.5)	23 (16.5)
PIPJ 4	15 (3.7)	21 (5.7)	37 (10.6)	55 (15.5)	28 (12.5)	22 (15.8)
PIPJ 5	23 (5.6)	20 (5.4)	27 (7.7)	50 (14.1)	33 (14.7)	26 (18.7)
Wrist	2 (0.5)	1 (0.3)	12 (3.6)	7 (2.0)	8 (3.7)	11 (8.1)
MTPJ 1	9 (2.2)	9 (2.4)	35 (10.4)	68 (19.9)	74 (33.6)	68 (48.6)
MTPJ 2	16 (3.9)	15 (4.1)	26 (7.7)	40 (11.7)	14 (6.4)	18 (12.9)
MTPJ 3	7 (1.7)	7 (1.9)	13 (3.9)	22 (6.4)	8 (3.6)	9 (6.4)
MTPJ 4	4 (1.0)	10 (2.7)	16 (4.8)	20 (5.8)	12 (5.5)	7 (5.0)
MTPJ 5	24 (5.9)	16 (4.3)	30 (8.9)	32 (9.4)	24 (10.9)	14 (10.0)

Table 3-33 Prevalence of grade ≥ 1 osteophytes in healthy subjects according to age deciles

MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; G, grade; Os, osteophyte

3.3.8 Erosions

Then presence of erosions on ultrasound were only examined in MCPJ 2 and 5 and MTPJ 5. There was a low prevalence of erosions across the age groups, with the most prevalent site for erosions being MCPJ 2 in the HS O age group at just 1.9% (Table 3-34 and Figure 3-9). No healthy subjects in the youngest age group had erosions in MTPJ 5 and the prevalence was still very low in the other two age groups.

	HS Y (18-39 years)	**HS M (40-59 years)**	**HS O (60-80 years)**
	Present n (%)	Present n (%)	Present n (%)
MCPJ 2 Er	4 (0.5)	5 (0.8)	7 (1.9)
MCPJ 5 Er	6 (0.8)	4 (0.6)	2 (0.6)
MTPJ 5 Er	0 (0.0)	5 (0.8)	1 (0.3)

Table 3-34 Presence of erosions on ultrasound in metacarpophalangeal joints 2 and 5 and metatarsophalangeal joint 5 in healthy subjects

HS Y, young healthy subjects (18-39 years old); HS M, middle healthy subjects (40-59 years old); HS O, old healthy subjects (60-80 years old); MCPJ, metacarpophalangeal joint; MTPJ, metatarsophalangeal joint; Er, erosion

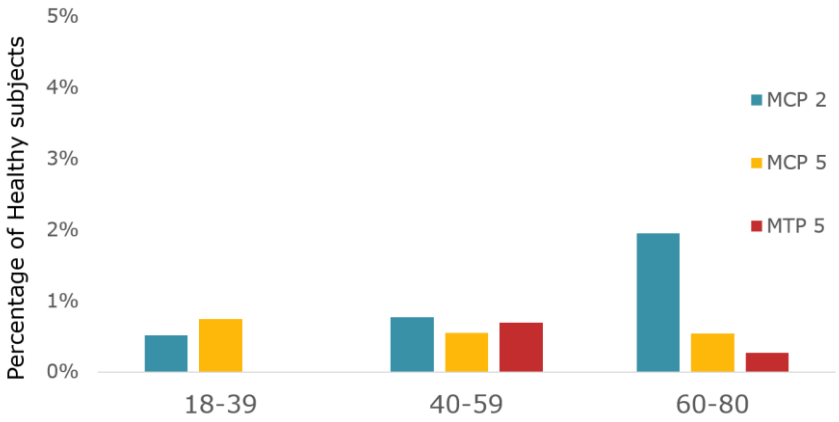

Figure 3-9 Column chart of percentage of healthy subjects with presence of erosions in metacarpophalangeal joints 2 and 5 and metatarsophalangeal joint 5

MCPJ, metacarpophalangeal joint; MTPJ, metatarsophalangeal joint

3.3.9 Binomial logistic regression analysis

To examine the effect of age on prevalence on SH grade ≥1 binomial logistic regression analysis was performed with these possibly significant confounding variables: age, gender, BMI, smoking status and manual occupation. After cases with missing information for these variables were excluded there were 1765 cases observed for SH grade ≥1 in each joint by binomial logistic regression analysis.

	Age				Female				BMI				Smoking (ever)				Manual occupation			
	B	P	OR	CI	B	P	OR	CI	B	P	OR	CI	B	P	OR	CI	B	P	OR	CI
MCP 1	0.07	0.25	1.00	1.00-1.02	-0.48	0.03	1.62	0.40-0.96	0.02	0.36	0.62	0.98-1.07	-0.23	0.26	0.80	0.54-1.18	-0.62	0.04	0.54	0.30-0.98
MCP 2	0.02	0.00	1.02	1-01-1.04	-0.35	0.10	1.43	0.46-1.08	0.02	0.42	1.02	0.98-1.06	-0.19	0.34	0.83	0.56-1.22	-0.94	0.00	0.39	0.23-0.66
MCP 3	0.03	0.00	1.03	1.01-1.04	-0.42	0.11	0.66	0.39-1.11	0.05	0.05	1.05	1.00-1 11	-0.25	0.29	0.78	0.49-1.24	-1.37	0.00	0.26	0.15-0.45
MCP 4	0.03	0.00	1.03	1.01-1.05	-0.01	0.98	0.99	0.56-1.76	0.08	0.01	1.08	1.03-1 15	0.06	0.82	1.07	0.61-1.87	0.98	0.01	0.38	0.19-0.74
MCP 5	0.02	0.03	1.02	1.00-1.05	-0.06	0.86	0.94	0.48-1.85	0.04	0.23	1.04	0.97-1 12	-0.48	0.13	0.62	0.33-1.16	-0.98	0.02	0.38	0.17-0.83
PIP 1	0.05	0.00	1.05	1.03-1.07	-0.42	0.24	0.66	0.33-1.33	0.06	0.05	1.06	1.00-1 13	0 99	0.01	2.69	1.24-5.85	-0.70	0.09	0.50	0.22-1.11
PIP 2	0.03	0.02	1.03	1.01-1.05	0.27	0.45	1.31	0.65-2.67	0.09	0.02	1.09	1.02-1 17	0 30	0.44	1.35	0.64-2.84	0.05	0.92	1.06	0.35-3.19
PIP 3	0.03	0.01	1.03	1.01-1.05	0.24	0.47	1.27	0.67-2.42	0.08	0.01	1.08	1.02-1 16	-0.12	0.71	0.89	0.47-1.67	0.07	0.89	1.07	0.40-2.90
PIP 4	0.02	0.09	1.02	1.00-1.04	0.40	0.23	1.50	0.78-2.88	0.07	0.04	1.08	1.01-1 15	0.77	0.06	2.16	0.97-4.77	-0.41	0.40	0.67	0.26-1.71
PIP 5	0.03	0.07	1.03	1.00-1.06	-0.72	0.26	0.49	0.14-1.70	0.06	0.23	1.06	0.96-1 16	1 37	0.07	3.92	0.90-17.1	0.55	0.60	1.73	0.22-13.6
Wrist	0.02	0.00	1.02	1.01-1.03	-0.35	0.03	0.71	0.52-0.96	-0.03	0.13	0.98	0.94-1.01	-0.00	0.99	1.00	0.75-1.33	-0.19	0.45	0.83	0.51-1.35
MTP 1	0.02	0.00	1.02	1.01-1.03	0.40	0.00	1.49	1.20-1.85	-0.03	0.03	0.98	0.95-1.00	-0.25	0.02	0.78	0.63-0.96	0.03	0.87	1.04	0.70-1.53
MTP 2	0.00	0.45	1.00	1.00-1.01	-0.10	0.39	0.90	0.71-1.14	0.01	0.63	1.01	0.98-1.03	-0.13	0.29	0.88	0.70-1.11	-0.48	0.02	1.62	0.42-0.92
MTP 3	0.00	0.72	1.00	0 99-1.01	0.15	0.24	1.17	0.90-1.50	0.04	0.00	1.04	1.02-1.07	-0.05	0.69	0 95	0.73-1.23	-0.22	0.33	0.81	0.52-1.25
MTP 4	0.01	0.03	1.01	1.00-1.02	0.31	0.04	1.37	1.02-1.84	0.04	0.01	1.04	1.01-1.08	-0.01	0.94	0 99	0.73-1.34	-0.11	0.66	0.89	0.54-1.47
MTP 5	-0.01	0.40	0.99	0 97-1.01	0.05	0.89	1.05	0.52-2.14	0.02	0.61	1.02	0.94-1 11	0 34	0.39	1.41	0.65-3.07	-1.45	0.00	0.24	0.10-0.58

Table 3-35 Binary logistic regression analysis for synovial hypertrophy grade ≥ 1 in metacarpophalangeal, proximal interphalangeal, wrist and metatarsophalangeal joints

MCP, metacarpophalangeal joints; PIP, proximal interphalangeal joints; MTP, metatarsophalangeal joints; BMI, body mass index; B, unstandardized coefficient; P, p value, OR, odds ratio, CI, confidence intervals

Age survived correction with the other variables of gender, BMI, smoking and manual occupation, and was significantly associated with proportion of SH grade ≥ 1 in MCPJ 2-4, PIPJ 1 and 3, wrist and MTPJ 1 ($p<0.001$), and at a lower level of significance in MCPJ 5, PIPJ 2, and MTPJ 4 ($p<0.05$).

Contrary to what might be expected, HS who were not working in or retired from manual occupations had significantly higher proportion of SH grade ≥1 in MCPJ 2 and 3, and MTP 5 ($p<0.01$). This may suggest that use of hand and feet may be protective of abnormal synovial hypertrophy of joints. SH grade ≥1 in PIPJ 1 which was significantly higher in the manual occupation group in Table 3-20 is not significant for manual occupation in this analysis, and this association may have been contributed to by age or smoking history ($p<0.01$).

BMI was significantly associated with SH grade ≥1 in MTPJ 3 and 4 ($p<0.01$), which is likely due to the effect of increased weight loading through these joints.

3.3.10 Summary

This is the largest study of ultrasound of hand, foot and wrist joints in healthy subjects. Although a lot of these healthy subjects were in the younger age group, there were many in the older two age groups which encompass the age range in which RA typically presents. There were significantly more grade ≥1 SH, PD, EF and Os in HS in the older age groups as expected. There were very low levels of PD in all joints scanned, even in the oldest age group, supporting that when PD is detected it is unlikely to be incidental or age related.

The data in this study should help guide Rheumatology sonographers to interpret ultrasound findings in the context of the age of the patient. If the prevalence of grade 1 findings are >5%

in a specific joint in an age group, then this could be regarded as an age-related finding and for it to be considered pathological it should be grade ≥2. The following lists summarise the grades at each joint level which could be considered abnormal according to age groups.

Metacarpophalangeal joints

- SH grade ≥2 in MCPJ 1-3 in 40-59 year olds
- SH grade ≥2 in MCPJ 2-4 in 60-80 year olds
- PD grade ≥1 in MCPJ 1-5 in all age groups
- EF grade ≥2 in MCPJ 1-5 in all age groups except MCPJ 5 in 18-59 year olds

Proximal interphalangeal joints

- SH grade ≥1 in PIPJ 1-5 in all age groups
- PD grade ≥1 in PIPJ 1-5 in all age groups
- EF grade ≥2 in PIPJ 1 in all age groups
- EF grade ≥2 in PIPJ 2-4 in 60-80 year olds

Metatarsophalangeal joints

- SH grade 3 in MTPJ 1-3 in all age groups, and MTP 4 in 40-80 year olds
- PD grade ≥1 in MTPJ 1-5 in all age groups
- EF grade 3 in MTPJ 1 and 2 in all age groups
- EF grade 3 in MTP 3 in 40-80 year olds
- EF grade 3 in MTP 4 in 60-80 year olds

Wrist joints

- SH grade ≥2 in wrists in all age groups
- PD grade ≥1 in wrists in all age groups
- EF grade ≥2 in wrists in all age groups

The MTPJs appeared to be susceptible to more grade ≥1 SH in HS with higher BMI, so this should be taken in to consideration when scanning MTPJs. EF was also very common in the MTPJs of HS across the age range, so the presence of PD grade ≥1 is the only helpful abnormal MSUS finding in the MTPJs.

There were unexpectedly high levels of SH grade ≥1 in wrist and MTP joints. This has led to further reliability studies in section 3.4 and development of wrist and MTPJ ultrasound atlases in section 3.5.

3.4 Overcoming reliability issues

The inter-observer reliability of ultrasound scans performed in this study had been initially addressed by one experienced sonographer in the Birmingham centre reviewing the ultrasound images from the first HS recruited by each centre to ensure that centres were grading in the same way. All contributors were based in experienced ultrasound centres that had participated in previous OMERACT studies. When receiving the results it became apparent that data from some individual centres had much higher grades when compared to others. To further address reliability issues it was decided that individual centre data should be compared.

3.4.1 Round 1 of reliability studies

The first round of reliability studies for centres was performed in May 2018 when data from 17 centres had been collected. Synovial hypertrophy grade ≥1 was chosen as the ultrasound abnormality to compare between recruiting centres because prevalence of PD grade ≥ 1 was low across all recruiting centres. Also low grade joint effusion in isolation is commonly not regarded as pathological. The joints with highest prevalence of grade ≥1 SH were: MCPJ 1-3, PIPJ 1, wrists, MTPJ 1-4. Some centres had recruited predominantly HS in the 18-39 years age

range, whilst others had mostly older HS, so scatter graphs of grade ≥1 SH in these joints were plotted by age for each individual centre to examine if age was the cause of the variation in prevalence of grade ≥1 SH.

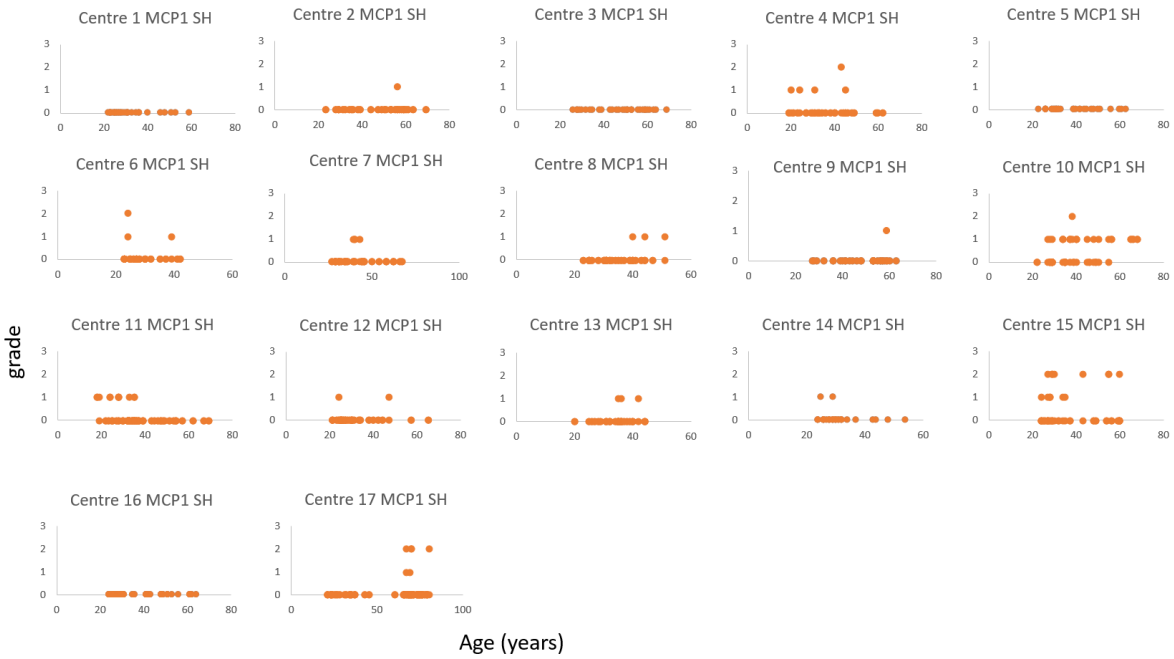

Figure 3-10 Synovial hypertrophy grade 0-3 in metacarpophalangeal joint 1 by contributing centres and age of healthy subjects in years

The graphs in Figure 3-10 and 3-11 represents SH graded by all centres in MCPJ 1 and the wrist, but similar graphs were plotted for MCPJ 2 and 3, PIPJ 1, and MTPJ 1-4. Two centres appeared anomalous in Figure 3-10 (centre 10 and centre 15). Unfortunately the ultrasound images from centre 10 were not available to be centrally regraded due to a hard drive failure. It was decided to exclude this centre from the final data analysis. The wrist graphs showed that grade 1 SH in the wrist was common in some centres even in the younger HS, and there were some centres that recorded grade 3 SH. This is unexpected in healthy individuals. These graphs highlighted the need for further reliability studies which were carried out after all HS were recruited, acknowledging that an option to centrally score the images if required was available.

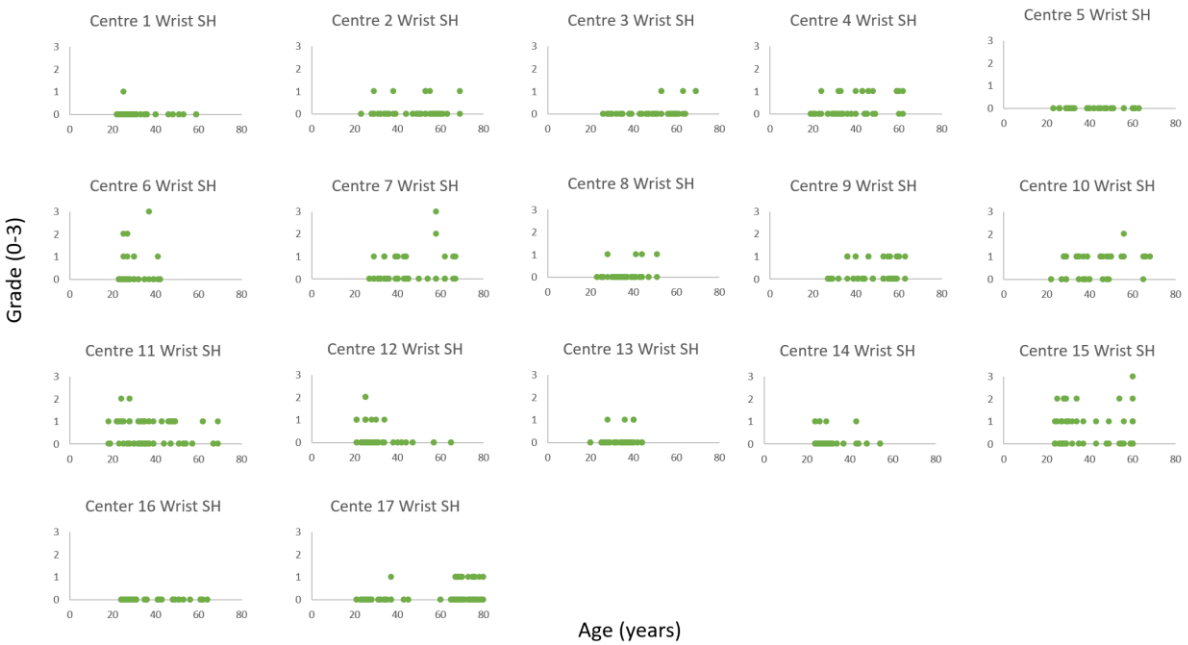

Figure 3-11 Synovial hypertrophy grade 0-3 in the wrist by contributing centres and age of healthy subjects in years

SH, synovial hypertrophy

Power Doppler prevalence by grade was plotted for the wrist joints because PD was more common in these joints than others. There were few centres that graded HS with PD ≥ 1, and in those that did the HS appeared to be in the older age ranges (Figure 3-12).

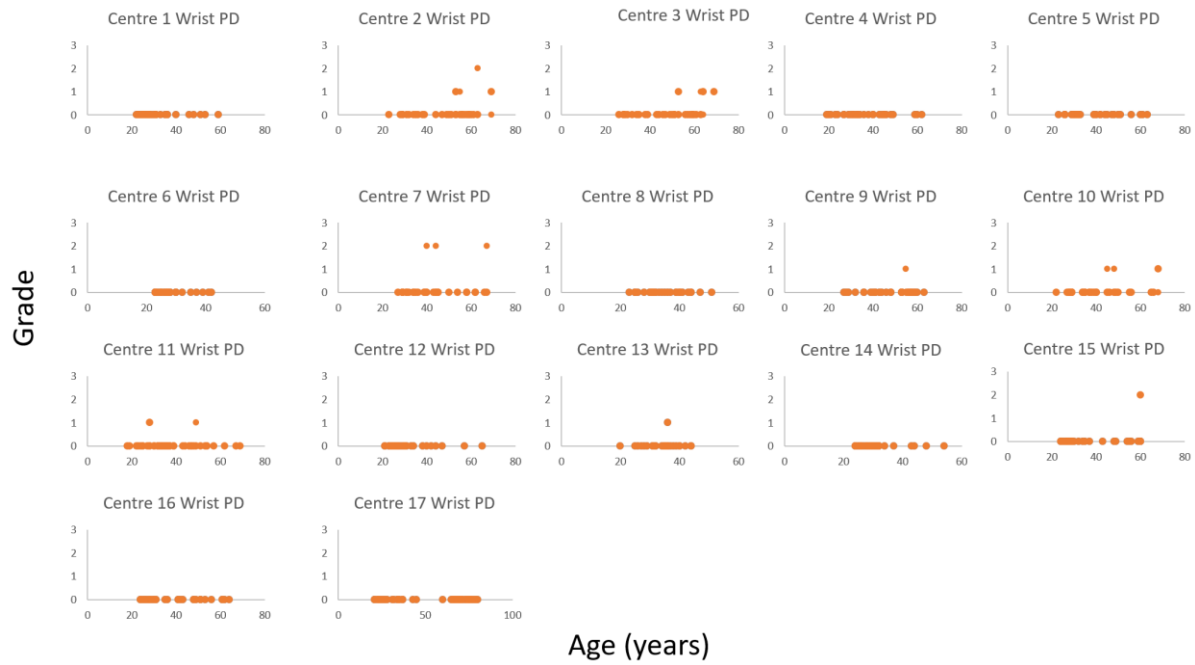

Figure 3-12 Power Doppler grade 0-3 in the wrist by contributing centres and age of healthy subjects in years

PD, Power Doppler

3.4.2 Round 2 of reliability studies

Following the second round of HS recruitment there were 21 centres participating in this study. The median ages of HS in each centre in Table 3-36 highlights the wide variation in ages of HS between recruiting centres which may have contributed to any differences seen in the prevalence of ultrasound abnormalities.

Anonymised centre number	Number recruited	Median age, years (IQR)
1	44	35.5 (26.3, 57.8)
2	29	34.0 (28.0, 45.0)
3	90	69.5 (52.5, 73.3)
4	42	39.5 (31.0, 58.5)
5	44	45.5 (31.0, 55.5)
6	36	53.0 (41.0, 57.8)
7	84	51.5 (39.5, 58.0)
8	45	43.0 (30.5, 53.0)
9	30	31.5 (26.8, 42.3)
10	46	52.0 (45.8, 56.0)
11	45	34.0 (25.5, 46.0)
12	42	36.5 (33.5, 44.0)
13	22	50.5 (35.3, 58.8)
14	54	32.0 (22.8, 54.3)
15	44	45.0 (34.3, 54.0)
16	45	45.0 (28.5, 56.5)
17	45	32.0 (28.0, 53.0)
18	74	36.0 (32.8 (50.3)
19	20	63.0 (58.8, 71.8)
20	45	30.0 (25.0, 41.5)
21	28	28.5 (24.0, 38.8)
Total	**954**	**43.0 (31.0, 57.0)**

Table 3-36 Median ages of healthy subjects recruited by each centre
IQR, interquartile range

The graphs of SH grade ≥ 1 in MCP and PIP joints 1-5 in Figure 3-13 show the majority of SH grade ≥1 was less than 10% across all centres. There were a few centres with high prevalence of grade 2 SH such as centre 14 for MCPJ 1 and centre 16 for MCPJ 1. These centres had mean ages of 32 and 45 years respectively.

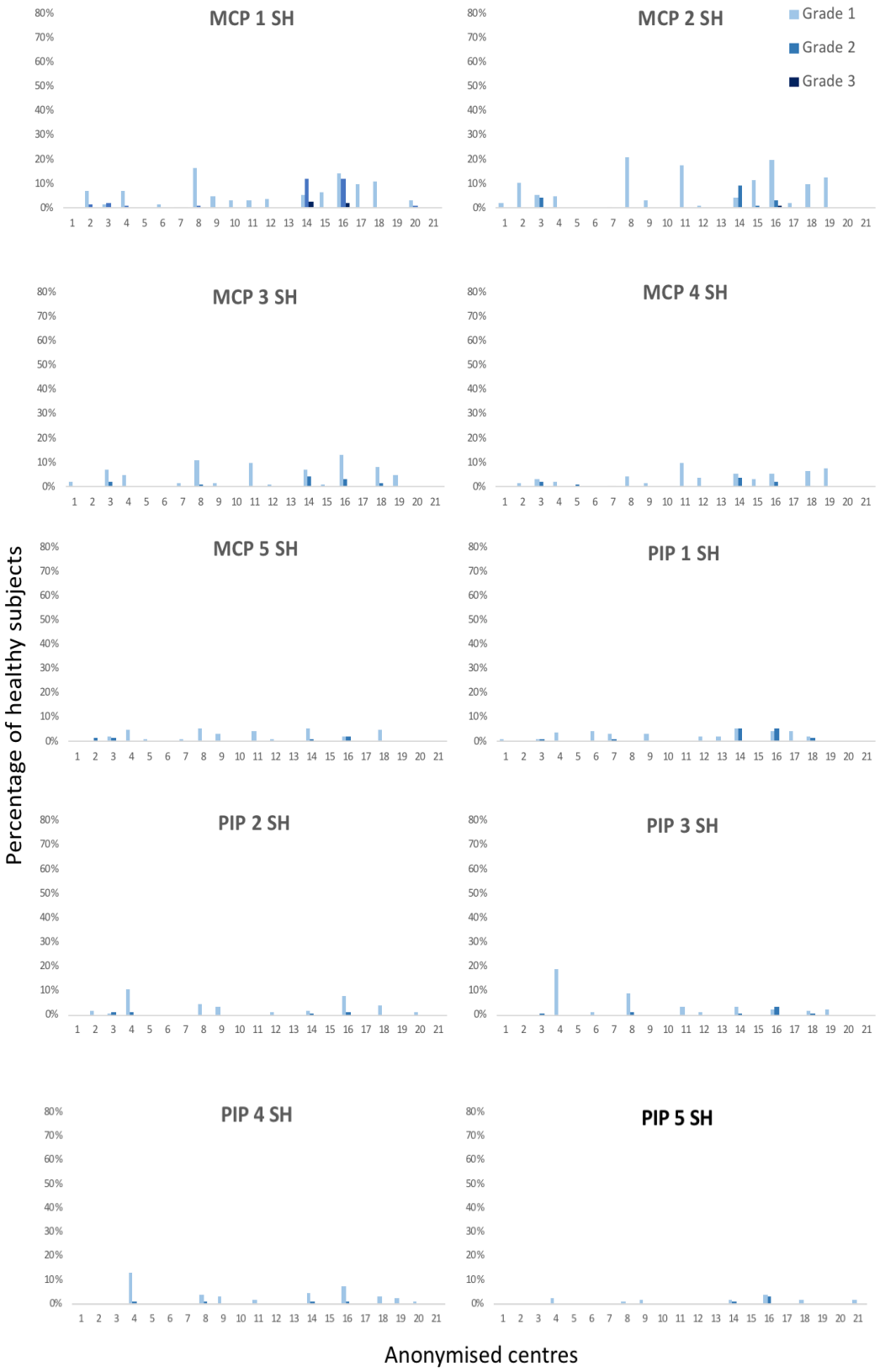

Figure 3-13 Comparison of proportion of synovial hypertrophy in metacarpophalangeal and interphalangeal joints 1-5 and wrist joints between recruiting centres

SH, synovial hypertrophy; MCP, metacarpophalangeal joint, PIP proximal interphalangeal joint

The charts of SH grade ≥ 1 in MTPJ 1-5 and wrist joints in Figure 3-14 show higher prevalence of SH grade ≥1 in most centres with the exception of MTPJ 5 which had low proportions graded by all centres.

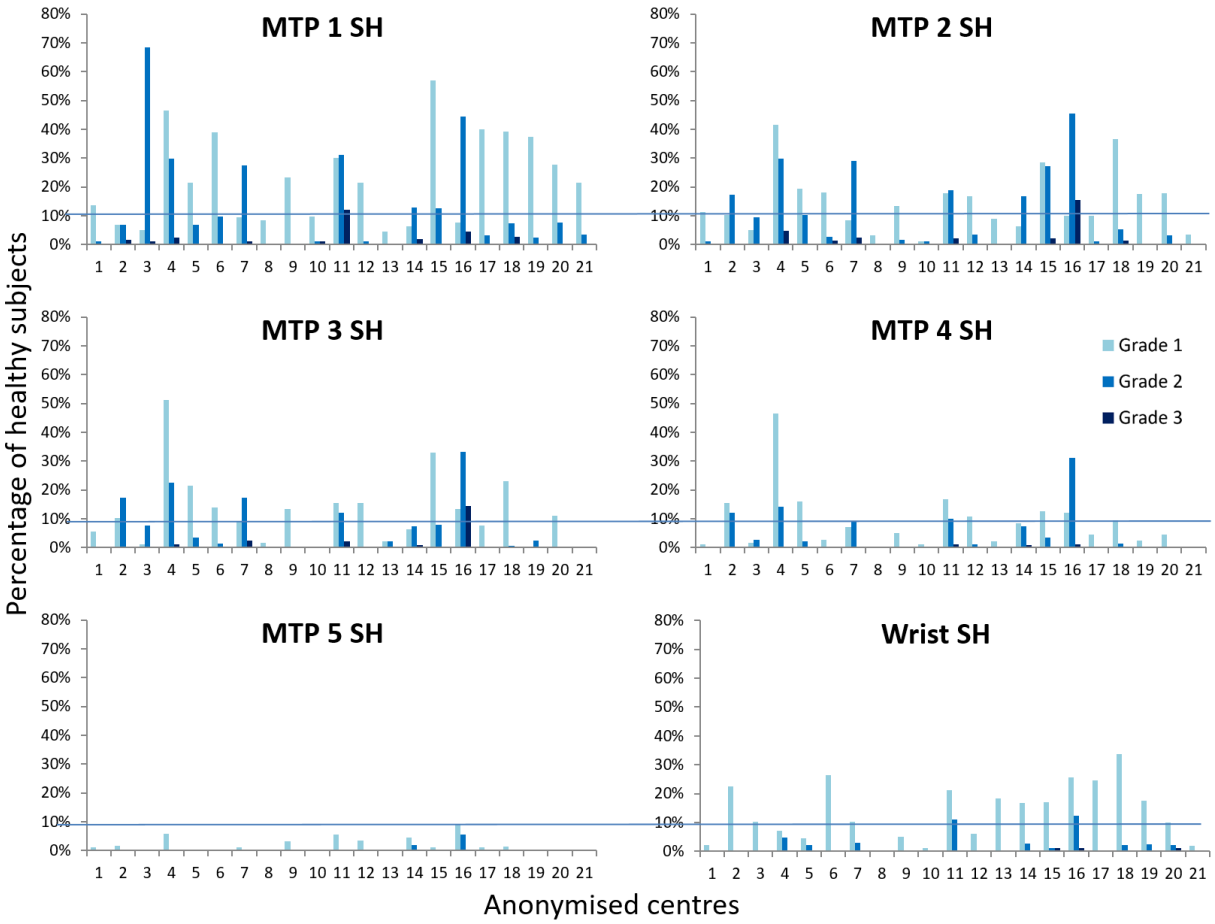

Figure 3-14 Comparison of proportion of synovial hypertrophy in metatarsophalangeal joints 1-5 and wrist joints between recruiting centres

SH, synovial hypertrophy; MTP, metatarsophalangeal joint

There was most disparity in the prevalence of SH grade ≥1 in wrist and MTP joints between all centres. In order to determine the source of the inconsistencies in prevalence of MTPJ and wrist SH grade ≥1, it was decided these joints would be the focus of a central regrading exercise. Three centres with high proportion of SH grade ≥ 1 in the MTP joints and two centres with high proportion of SH grade ≥ 1 in the wrist joints were selected to be centrally regraded (Figures 3-15 and 3-16).

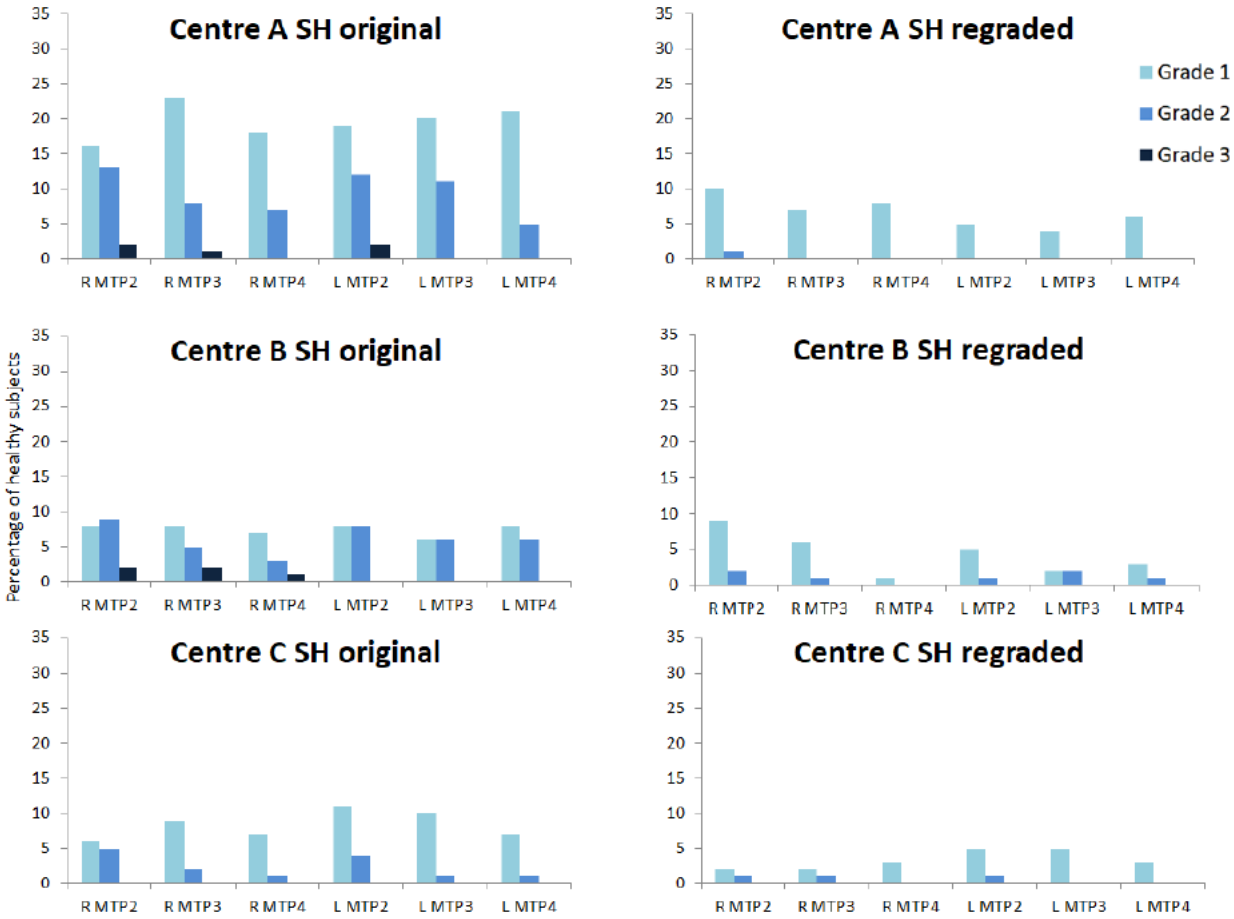

Figure 3-15 Proportion of original and regraded synovial hypertrophy grade ≥ 1 in metatarsophalangeal joints 2-4

SH, synovial hypertrophy; MTP, metatarsophalangeal joint; R, right; L, left

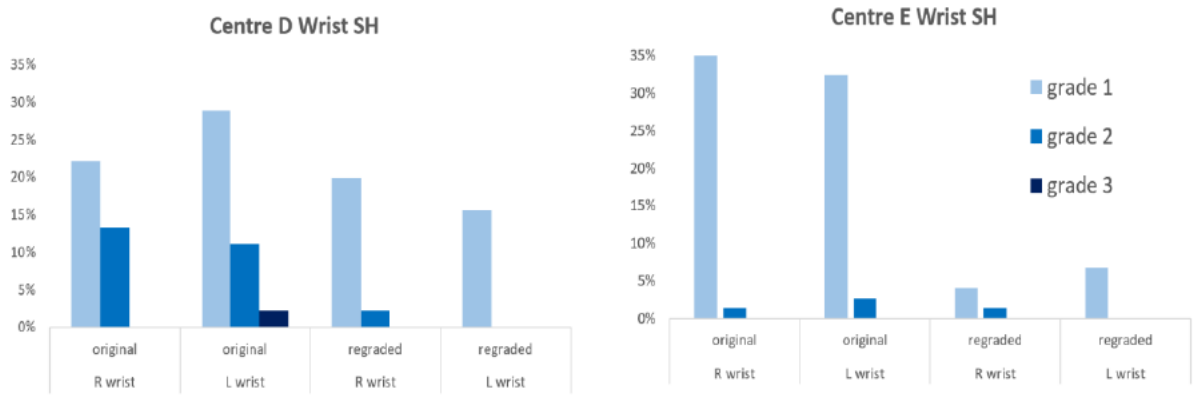

Figure 3-16 Proportion of original and regraded synovial hypertrophy grade ≥ 1 in wrist joints

SH, synovial hypertrophy; R, right; L, left

The graphs in Figures 3-15 and 3-16 show marked differences, with the regraded SH for MTP and wrist joints being much lower. This striking difference has raised doubt that sonographers contributing to this study were grading MTP and wrist joints consistently and has highlighted the need for a thorough regrading of all images from all centres. It was initially considered to ask centres with levels of SH grade ≥1 above 10% in the wrist and MTPJs (shown in Figure 3-14) to regrade their images based on new atlases of MTP and wrist joints (see section 3.5). However, it was later decided that all images from all centres would be regraded by sonographers from the hub centre to assess reliability.

3.4.3 Summary

High levels of inter-centre variability were seen, particularly for proportions of SH grade ≥1 in MTP 1-5 and wrist joints. Proportions of SH grade ≥1 in MCP and PIP joint were more consistent between centres. Graphs were plotted to look at the effect of distributions of ages of HS in centres but this did not appear to account for the differences seen. This led to the question of whether the underlying reason for this was due a lack of consistency of ultrasound grading.

A selection of centres with the highest proportions of MTPJ and wrist SH grade ≥1 were selected for central regrading. The result of this suggested that centres were not grading MTPJs and wrists consistently. The pilot regrading of MTP or wrist joints from five centres has led to the decision to regrade all the images centrally. The scope of this is beyond my thesis and is still on going. It has also highlighted that the EULAR-OMERACT consensus grading publications primarily focus on the MCP and PIP joints, with image examples of grades for these joints. There is little or no specific guidance in these consensus gradings with regards to the MTP and wrists joints which are anatomically very different from the MCP and PIP joints.

This has highlighted the need for new atlases to clarify the grading of synovial hypertrophy in these joints as they are very different to MCP and PIP joints.

3.5 Generating atlases of wrist and metatarsophalangeal joints

3.5.1 Need for new atlases

The consideration of reliability in section 3.4 highlighted that wrist and MTP joints were being graded differently between the experienced participating ultrasound centres. The protocol used to recruit and scan healthy subjects gave details of how to grade each joint and each ultrasound parameter according to the EULAR OMERACT grading consensus.[207] This consensus and the protocol for this study (see Appendix 1) contained example images of grades of synovial hypertrophy, effusion and Power Doppler in MCP joints. Further references to atlases for the PIP, wrist and MTP joints were given in the protocol and all ultrasound centres participating in this study were experienced OMERACT centres who had contributed to the creation of the EULAR-OMERACT grading consensus.

On review, the atlases specified in the OMERACT papers [212] [213] contain only a single example image of wrist and MTP joints for each grade. It was therefore decided that using the images collected from this study may help Rheumatology sonographers in future to better define the grade 0 and 1 SH changes in wrist and MTP joints.

3.5.2 First stage of creation of atlases

Atlases were compiled according to the methods in 3.2.6 and sent out to the wider group. The atlases generated much discussion, with some images being regraded after consensus reached.

The earlier versions of the wrist and MTP atlases contained “borderline images” of joints that could be graded 0 or 1 (termed grade 0+), or grade 1 or 2 (termed grade 1+). However, feedback from the other participating centres concluded this was confusing as it could be misconstrued as proposing a new grading system.

An anatomical description of how to distinguish grade 1 from grade 2 or 3 synovial hypertrophy in the radio-carpal and inter-carpal joints was proposed, with grade 1 SH not crossing a horizontal line drawn from the shaft of the radius. The other centres felt this was a helpful guide but needed further clarity.

The early atlases included scanning positions for the MTP joints which are commonly hyper-extended or subluxed when the foot is at rest. This may exaggerate the true extent of the SH leading to falsely high ultrasound gradings. To rectify this the toe should be straightened into a neutral position. The feedback from the wider group was that clarity was also needed on scanning position for the wrists.

3.5.3 Second stage of creation of atlases

The current wrist and MTP joint atlases can be found in Appendix 2. These atlases included a section at the beginning with recommendations on the approach to ultrasound grading with: positioning of the patient for scanning to ensure neutral alignment of the joint; identifying the extent of the joint capsule or recess enlargement; distinguishing synovial tissue from effusion, tendon or dorsal plate; and examining the echogenicity of the synovial tissue. This last recommendation was contentious; it proposed that if the tissue appeared hypoechoic (meaning the image has areas which appear dark grey) then this should be interpreted as inflammation. If it appears iso-echoic (grey and homogenous) or hyperechoic (white) then this represents

chronically inflamed tissue and should not be graded. The issue of echogenicity is contentious, and many of the other participating OMERACT centres did not agree with this as a parameter for grading joints. One point raised was that there is not enough evidence that hypoechoic areas on ultrasound represent acutely inflamed synovial tissue, and it would be very time consuming in clinical practice. After much debate it was decided that evaluation of echogenicity would be excluded from the final atlas used to centrally regrade the images.

Borderline images were not included in the final atlases because the group feedback indicated they were confusing. Instead guidance was given on common pitfalls to avoid, and multiple images of each grade 0-3 were included to further illustrate how to grade these joints.

3.5.4 Wrist atlas common pitfalls and grading guidance

The wrist atlases include image examples of neutral positioning for scanning, and also hyper-extension and hyperflexion which should be avoided because they can skew ultrasound grading. The transverse ligament in the radio-carpal recess can often be mistaken for a hypoechoic area of synovial hypertrophy, therefore images highlighting this pitfall to avoid were included (Figure 3-17).

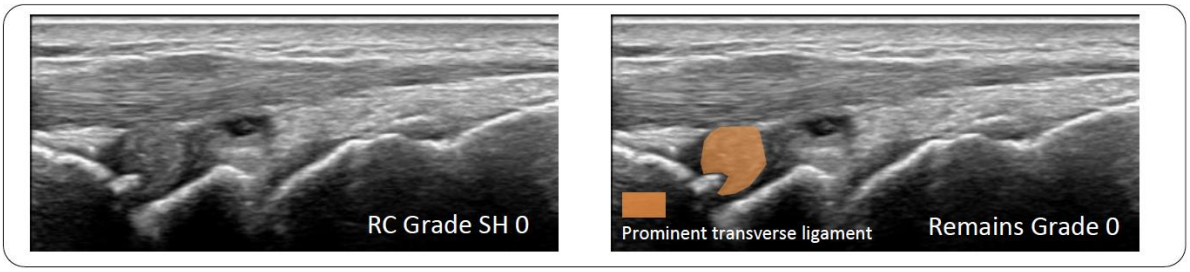

Figure 3-17 Prominent transverse ligament in wrist radio-carpal recess
SH, synovial hypertrophy

When creating the wrist atlas it was decided that a description of how to distinguish grade 1, 2 and 3 SH was needed. In MCP joints a horizontal line between the distal metacarpal and proximal phalanx is used to demarcate where grade 1 finishes and grade 2 begins. A similar approach was applied to the grading of wrist radio-carpal and inter-carpal joints (Figure 3-18).

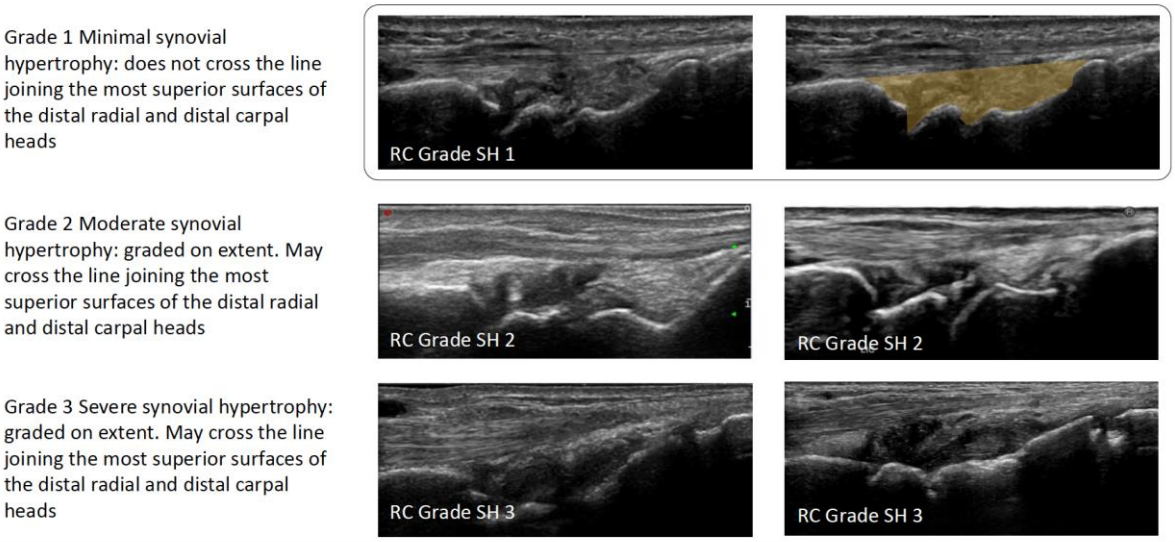

Figure 3-18 Wrist radio-carpal and intercarpal joint ultrasound grading based on extent of hypoechoic synovial tissue

RC, radio-carpal; SH, synovial hypertrophy

3.5.5 Metatarsophalangeal joint atlas common pitfalls and grading guidance

The issue of MTPJs commonly resting in hyperextension or subluxation was addressed with images to demonstrate neutral alignment and the effect that hyperextension may have on grading of SH (Figure 3-19)

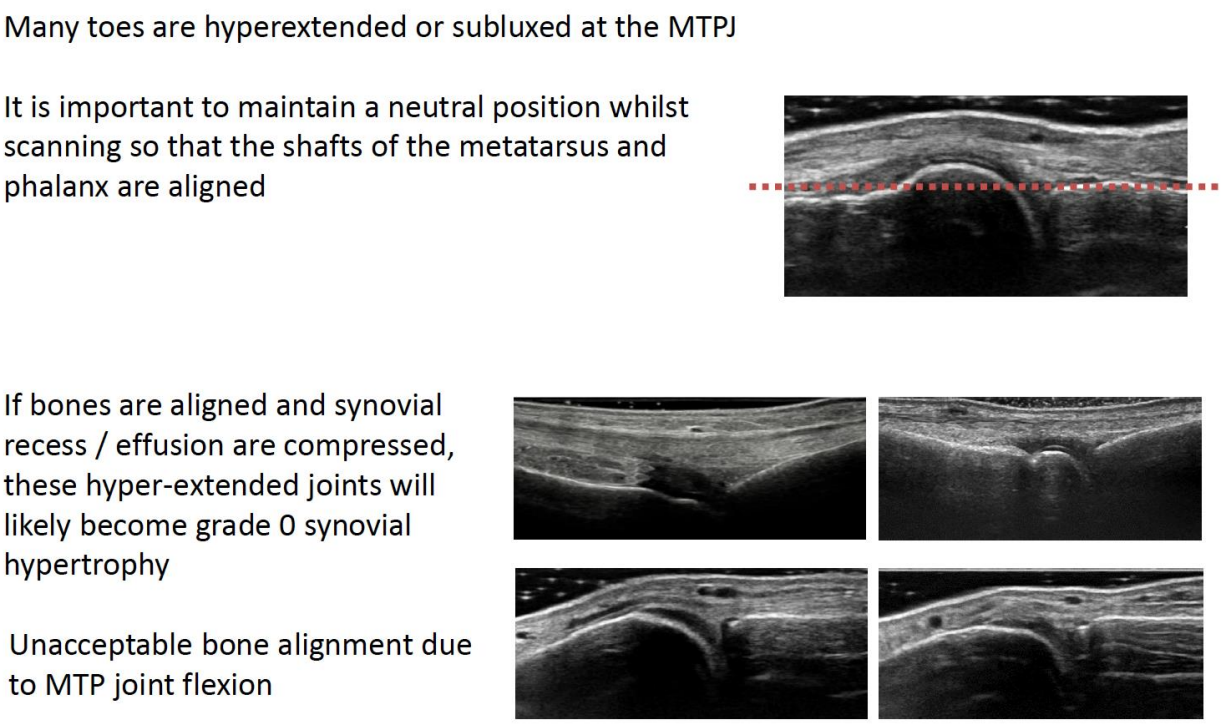

Figure 3-19 Alignment of metatarsophalangeal joints for ultrasound grading

A pitfall in grading SH in the first MTPJ is that the joint capsule extends proximally and when joint effusion is present. This may mislead the sonographer in to grading this as SH grade ≥1, when in fact the synovial tissue itself is normal (Figure 3-20). The dorsal plate or capsule complex may also be elevated by underlying joint effusion giving an image that may be falsely interpreted as synovial hypertrophy grade ≥ 1.

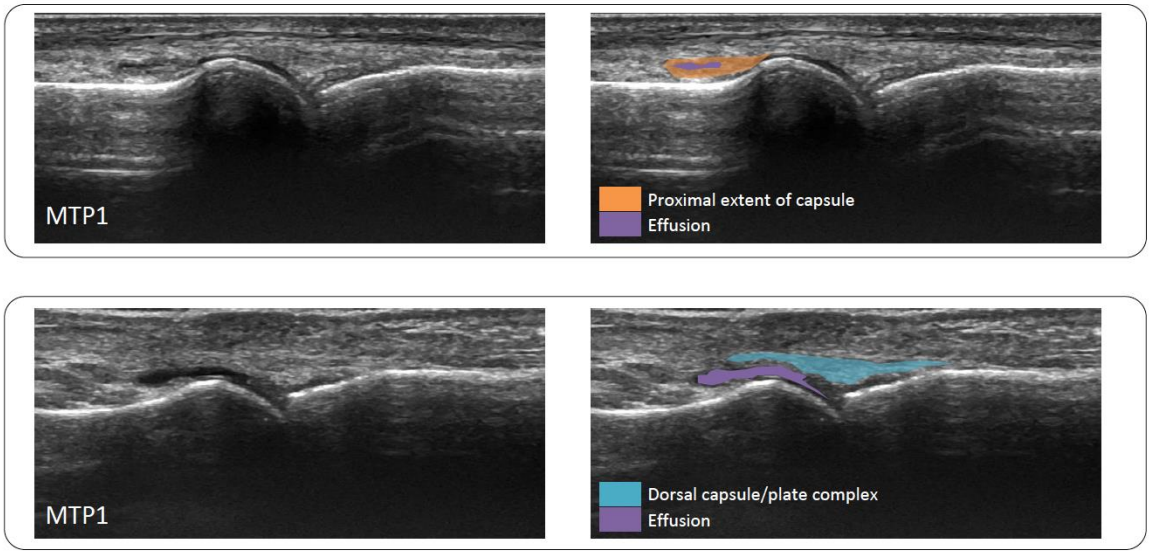

Figure 3-20 Metatarsophalangeal joint capsule and recess on ultrasound
MTP; metatarsophalangeal joint

3.5.6 Summary

The production of new MTP and wrist atlases from this project has been a large undertaking, with areas of controversy to resolve. This has been a useful exercise because it has helped to provide an insight into the various reasons why centres which have agreed on a consensus grading system have not graded consistently between centres in this large study. The decision has been made to regrade all the images from the minimal disease study centrally using the new atlases. This data will not be included in this thesis because this is still ongoing, but the regraded data will be used in the final published data.

3.6 Tendon ultrasound in healthy subjects and RA patients

3.6.1 Hypothesis

Low grades of tenosynovial hypertrophy are present in the older healthy population.

3.6.2 Objective

Determine the prevalence of ultrasound detected tendon abnormalities in healthy subjects (HS) across the age range and compare with a cohort of patients with early Rheumatoid Arthritis.

3.6.3 Results

One thousand and thirty-eight HS were recruited and 939 HS were included following exclusions detailed in 3.3.1.3 and an additional 15 HS were excluded compared to the joint data because ultrasound tendon data were missing from the second round of recruitment from one contributing centre. A comparison cohort of 144 RA patients were extracted from the BEACON database, and 144 HS were matched to these RA patients based on sex, age (within 2 years) and smoking status where possible.

3.6.3.1 Healthy subject demographics

The median age of HS was 43 years (IQR 30-57). For the purpose of statistical analysis HS were grouped into three age groups: HS Y (young, 18-39 years), HS M (middle, 40-59 years) and HS O (old, 60-80 years). A total of 11237 tendons were scanned in 939 HS; 98% of these tendons were grade 0 for all three ultrasound parameters of tenosynovial hypertrophy (TSH), Power Doppler within the tendon sheath (TPD) and tenosynovial effusion (TEF).

Prevalence of grade ≥1 TSH and TPD was low across the age range in HS. The demographics in Table 3-37 show that the comparison cohort of 144 age- and sex-matched HS had significantly lower mean BMI, and less smokers than the group of RA patients. There was significantly more TSH and TPD grade ≥1 in RA patients compared to age and sex-matched HS ($p<0.001$) except for TPD in DF 1 ($p=0.02$).

	HS Y 18-39 yr	HS M 40-59 yr	HS O ≥60 yr	HS Y/M/O p value	RA	RA vs age- and sex-matched HS # p value
n	405	350	184		144	
Age, years median (IQR)	29 (25-33)	49 (44-54)	68 (62-72)	<0.001	54 (45-67)	1.000
Females, n (%)	268 (66.2)	285 (81.4)	117 (63.6)	<0.001	106 (73.6)	0.924
BMI median (IQR)	23 (22-24)	25 (21-28)	26 (23-28)	<0.001	27 (24-32)	<0.001
Smoking						
never (%)	316 (78)	241 (68)	115 (63)		68 (47)	0.021
ever (%)	88 (22)	109 (31)	66 (36)		75 (52)	
current (%)	47 (12)	56 (16)	12 (7)		28 (19)	
EMS, minutes median (IQR)	n/a	n/a	n/a	n/a	60 (15-120)	n/a
Symptom duration, weeks median (IQR)	n/a	n/a	n/a	n/a	26 (13-52)	n/a
CRP, mg/L median (IQR)	n/a	n/a	n/a	n/a	7 (3-20)	n/a
DAS 28 CRP median (IQR)	n/a	n/a	n/a	n/a	5.1 (4.1-5.8)	n/a
Tender joint* median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	n/a	17 (11-27)	<0.001
Swollen joint* median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	n/a	6 (3-11)	<0.001
DF 1 TSH grade ≥1 n (%)	1 (0.1)	0 (0)	1 (0.3)	0.490	15 (5.2)	< 0.001
DF 2 TSH grade ≥1 n (%)	1 (0.1)	2 (0.3)	0 (0)	0602	50 (17.3)	< 0.001
DF 3 TSH grade ≥1 n (%)	2 (0.2)	1 (0.1)	2 (0.6)	0.432	50 (17.3)	< 0.001
DF 4 TSH grade ≥1 n (%)	2 (0.2)	1 (0.1)	1 (0.3)	1.000	28 (9.8)	< 0.001
DF 5 TSH grade ≥1 n (%)	1 (0.1)	4 (0.6)	0 (0)	0.220	36 (12.5)	< 0.001
ECU TSH grade ≥1 n (%)	7 (0.9)	9 (1.3)	1 (0.3)	0.293	65 (22.6)	< 0.001
DF 1 TPD grade ≥1 n (%)	1 (0.1)	0 (0)	1 (0.3)	0.490	10 (3.5)	0.002
DF 2 TPD grade ≥1 n (%)	0 (0)	1 (0.1)	0 (0)	0.568	36 (12.6)	< 0.001
DF 3 TPD grade ≥1 n (%)	1 (0.1)	0 (0)	0 (0)	1.000	40 (13.9)	< 0.001
DF 4 TPD grade ≥1 n (%)	0 (0)	0 (0)	1 (0.3)	0.194	20 (7)	< 0.001
DF 5 TPD grade ≥1 n (%)	0 (0)	0 (0)	0 (0)	n/a	23 (8.1)	< 0.001
ECU TPD grade ≥1 n (%)	0 (0)	0 (0)	0 (0)	n/a	62 (21.7)	< 0.001

Table 3-37 Demographics and tendon ultrasound findings (grade 1-3 tenosynovial hypertrophy and power Doppler) for healthy subjects and Rheumatoid Arthritis patients

HS, healthy subjects; RA, Rheumatoid Arthritis; IQR, interquartile range; yr, years; BMI, body mass index; EMS, early morning stiffness; CRP, C reactive protein; DAS 28, disease activity score; DF, digit flexor tendon, ECU, extensor carpi ulnaris tendon; TSH, tenosynovial hypertrophy; TPD, power Doppler within tendon sheath.

#RA and HS age and sex matched to compare ultrasound graded tendon findings.

*RA patients had 66/68 joint counts. HS had joint counts of MCPs, PIPs, wrists and MTPs.

3.6.3.2 Symmetry of tendon findings

The distribution of tendon abnormalities was symmetrical with no significant difference between right and left hands (Table 3-38). This supports our analysis of individual tendon data regardless of side of tendon.

	HS Y (18-39 yrs)		HS M (40-59 yrs)		HS O (60-80 yrs)		All age groups		
	Left n (%) G ≥ 1	Right n (%) G ≥ 1	Left n (%) G ≥ 1	Right n (%) G ≥ 1	Left n (%) G ≥ 1	Right n (%) G ≥ 1	Left n (%) G ≥ 1	Right n (%) G ≥ 1	p value* L vs R
TSH									
DF1	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)	1 (0.1)	1.000
DF2	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	1.000
DF3	1 (0.2)	1 (0.2)	1 (0.3)	0 (0.0)	1 (0.5)	1 (0.6)	3 (0.3)	2 (0.2)	1.000
DF4	1 (0.2)	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)	2 (0.2)	1.000
DF5	1 (0.2)	0 (0.0)	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	3 (0.3)	2 (0.2)	1.000
ECU	3 (0.7)	4 (1.0)	5 (1.4)	4 (1.1)	1 (0.6)	0 (0.0)	9 (1.0)	8 (0.9)	1.000
TPD									
DF1	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)	1 (0.1)	1.000
DF2	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	-
DF3	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	-
DF4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)	-
DF5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
ECU	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
TEF									
DF1	7 (1.7)	12 (3.0)	4 (1.1)	3 (0.8)	3 (1.6)	3 (1.6)	14 (1.5)	18 (1.9)	0.481
DF2	2 (0.5)	4 (1.0)	6 (1.7)	4 (1.1)	3 (1.6)	2 (1.1)	11 (1.2)	10 (1.1)	1.000
DF3	3 (0.7)	2 (0.5)	6 (1.7)	4 (1.1)	2 (1.1)	5 (2.7)	11 (1.2)	11 (1.2)	1.000
DF4	2 (0.5)	2 (0.5)	3 (0.8)	2 (0.6)	4 (2.2)	6 (3.2)	9 (1.0)	10 (1.1)	1.000
DF5	5 (1.2)	2 (0.5)	8 (2.2)	7 (1.9)	4 (2.2)	6 (3.2)	17 (1.8)	15 (1.6)	0.845
ECU	14 (3.5)	16 (4.)	9 (2.6)	9 (2.6)	3 (1.7)	6 (3.3)	26 (2.8)	31 (3.3)	0.442

Table 3-38 Distribution ultrasound findings of grade ≥ 1 in left and right tendons in healthy subjects

HS, healthy subject; G, grade; TSH, tenosynovial hypertrophy; TPD, power Doppler within tendon sheath; TEF, tenosynovial effusion; L, left; R, right. *Fisher's exact test

3.6.3.3 Ultrasound tendon findings in healthy subjects

There were no significant differences in prevalence of grade ≥1 TSH or TPD in DF tendons 1-5 or ECU tendons between the three age groups (Table 3-39). The tendon findings of TSH, TPD or TEF grade ≥1 across the 939 HS were of low severity, all being grade 1 with the exception of one grade 2 TSH in an ECU tendon. In HS, the ECU tendons had significantly

more TSH grade ≥1 when compared to each of the DF 1-5 tendons, with a prevalence of 0.9% in ECU tendon versus 0.1-0.3% in DF tendons 1-5 ($p<0.05$). However these numbers are so small it is difficult to draw firm conclusions despite the significant p values.

Tenosynovial effusion grade ≥1 in HS was more common than TSH or TPD grade ≥1 ($p<0.001$). There were significantly different proportions of TEF between age groups ($p<0.001$), however the highest percentage of grade ≥1 TEF in DF tendon 1 and in the ECU tendons were seen in the youngest age group, contrary to what might be expected which may be related to activity or normal physiology.

	HS Y (18-39 years)			HS M (40-59 years)			HS O (60-80 years)			p value* HS Y vs M vs O
	G 1 n (%)	**G 2 n (%)**	**G 3 n (%)**	**G 1 n (%)**	**G 2 n (%)**	**G 3 n (%)**	**G 1 n (%)**	**G 2 n (%)**	**G 3 n (%)**	
TSH										
DF 1	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0.490
DF 2	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0602
DF 3	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0.432
DF 4	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1.000
DF 5	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.220
ECU	7 (0.9)	0 (0.0)	0 (0.0)	8 (1.1)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0.293
TPD										
DF 1	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0.490
DF 2	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.568
DF 3	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
DF 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0.194
DF 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n/a
ECU	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n/a
	Present n (%)			**Present n (%)**			**Present n (%)**			
TEF										
DF 1	19 (2.3)			7 (1.0)			6 (1.7)			<0.001
DF 2	6 (0.7)			10 (1.4)			5 (1.4)			0.001
DF 3	5 (0.6)			10 (1.4)			7 (1.9)			<0.001
DF 4	4 (0.5)			5 (0.7)			10 (2.8)			<0.001
DF 5	7 (0.8)			15 (2.1)			10 (2.8)			<0.001
ECU	30 (3.7)			18 (2.6)			9 (2.5)			0.001

Table 3-39 Ultrasound tendon findings in healthy subjects

HS, healthy subject; G, grade; TSH, tenosynovial hypertrophy; TPD, power Doppler within the tendon sheath; TEF, tenosynovial effusion; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon.
* Fisher's exact test

3.6.3.4 Occupations and ultrasound tendon findings in healthy subjects

The previous joint ultrasound data in section 3.3.4 revealed the majority of volunteer HS were working in or retired from health care professionals such as doctors, nurses or other allied health care professionals (422/939, 44.9%, see Table 3-40). Other occupational groups included: secretaries or administrative staff (156/939, 16.6%); students (95/939, 10.1%); manual workers (including manual laborers and those with physically demanding services jobs such as cleaners) (68/939, 7.2%); and teachers (34/939, 3.6%).

Occupational groups	**n (%)**
Doctors	198 (21.4)
Nurses	173 (18.4)
Students	95 (10.1)
Administrative staff	92 (9.8)
Secretaries	60 (6.4)
Services *(of which manual workers)*	55 (5.9) *34 (3.6)*
Allied health care professionals	51 (5.4)
Scientists	49 (5.2)
Manual labourers	34 (3.6)
Teachers	32 (3.4)
Housewives	30 (3.2)
Finance	20 (2.1)
Academics	12 (1.3)
None	12 (1.3)
Managers	11 (1.2)
Engineers	5 (0.5)
Retired	5 (0.5)
Information technology	2 (0.2)
Lawyers	1 (0.1)
Architects	1 (0.1)
Unknown	1 (0.1)

Table 3-40 Occupations of healthy subjects

The proportions of TSH or TPD ≥ grade 1 in HS were observed in those currently working in or retired from manual occupations and compared to the rest of the HS (non-manual workers). There were no statistically significant differences, which may be due to the low numbers of ultrasound abnormalities seen in tendons, and the relatively small number of HS with manual occupations (Table 3-41).

	Manual workers Tendon number (%)	Non-manual workers Tendon number (%)	Manual vs non-manual workers p value*
Total number of tendons at each level	136	1735	
TSH			
DF 1 TSH G ≥ 1	1 (0.7)	1 (0.1)	0.140
DF 2 TSH G ≥ 1	0 (0.0)	3 (0.2)	1.000
DF 3 TSH G ≥ 1	0 (0.0)	5 (0.3)	1.000
DF 4 TSH G ≥ 1	0 (0.0)	4 (0.2)	1.000
DF 5 TSH G ≥ 1	0 (0.0)	5 (0.3)	1.000
ECU TSH G ≥ 1	1 (1.5)	16 (0.9)	1.000
TPD			
DF 1 TPD G ≥ 1	1 (0.7)	1 (0.1)	0.140
DF 2 TPD G ≥ 1	0 (0.0)	1 (0.1)	1.000
DF 3 TPD G ≥ 1	0 (0.0)	1 (0.1)	1.000
DF 4 TPD G ≥ 1	0 (0.0)	1 (0.1)	1.000
DF 5 TPD G ≥ 1	0 (0.0)	0 (0.0)	n/a
ECU TPD G ≥ 1	0 (0.0)	0 (0.0)	n/a
TEF			
DF 1 TEF G ≥ 1	5 (3.7)	27 (1.6)	0.175
DF 2 TEF G ≥ 1	2 (1.5)	19 (1.1)	0.768
DF 3 TEF G ≥ 1	0 (0.0)	22 (1.3)	0.588
DF 4 TEF G ≥ 1	0 (0.0)	19 (1.1)	0.583
DF 5 TEF G ≥ 1	3 (2.2)	29 (1.7)	0.658
ECU TEF G ≥ 1	4 (2.9)	52 (3.0)	1.000

Table 3-41 Ultrasound findings in healthy subjects: manual workers versus non-manual workers

HS, healthy subject; G, grade; THS, tenosynovial hypertrophy; TPD, power Doppler within the tendon sheath; TEF, tenosynovial effusion; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon. * Fisher's exact test

3.6.3.5 Physical hobbies and ultrasound tendon findings in healthy subjects

In section 3.3.5 the effects of physical hobbies on ultrasound findings in the joints were examined. Similarly, the proportions of grade ≥ 1 tendon ultrasound findings in those who practice sports or hobbies which may have high impact on the upper limbs such as weightlifting or boxing, were compared with those practising past times with low impact on the upper limbs. There were no statistically significant differences for grade ≥ 1 TSH, TPD or TEF in DF tendons 1-5. There were significant differences between the prevalence of grade ≥ 1 TSH and TEF in

ECU tendons at the low level ($p<0.05$), with grade ≥ 1 TSH more common in the older group of HS who were not practicing hobbies with high impact on upper limbs, and TEF more common in those younger HS practicing hobbies with high impact on upper limbs (Table 3-42).

	High impact upper limb hobbies Tendon Number (%)	Low impact upper limb hobbies Tendon Number (%)	p value*
Total number of tendons at each level	376	1502	
TSH			
DF 1 TSH G ≥ 1	1 (0.3)	1 (0.1)	0.361
DF 2 TSH G ≥ 1	0 (0.0)	3 (0.2)	1.000
DF 3 TSH G ≥ 1	0 (0.0)	5 (0.3)	0.590
DF 4 TSH G ≥ 1	0 (0.0)	4 (0.3)	0.590
DF 5 TSH G ≥ 1	0 (0.0)	5 (0.3)	0.590
ECU TSH G ≥ 1	0 (0.0)	17 (1.1)	0.033
TPD			
DF 1 TPD G ≥ 1	1 (0.3)	1 (0.1)	0.361
DF 2 TPD G ≥ 1	0 (0.0)	1 (0.1)	1.000
DF 3 TPD G ≥ 1	0 (0.0)	1 (0.1)	1.000
DF 4 TPD G ≥ 1	0 (0.0)	1 (0.1)	1.000
DF 5 TPD G ≥ 1	0 (0.0)	0 (0.0)	n/a
ECU TPD G ≥ 1	0 (0.0)	0 (0.0)	n/a
TEF			
DF 1 TEF G ≥ 1	3 (0.8)	29 (1.9)	0.199
DF 2 TEF G ≥ 1	1 (0.3)	20 (1.3)	0.145
DF 3 TEF G ≥ 1	1 (0.3)	21 (1.4)	0.123
DF 4 TEF G ≥ 1	1 (0.3)	18 (1.2)	0.189
DF 5 TEF G ≥ 1	3 (1.8)	29 (1.9)	0.199
ECU TEF G ≥ 1	18 (4.8)	39 (2.6)	0.049

Table 3-42 Ultrasound tendon findings in healthy subjects practicing hobbies with high impact versus low impact on the upper limbs

HS, healthy subject; G, grade; THS, tenosynovial hypertrophy; TPD, power Doppler within the tendon sheath; TEF, tenosynovial effusion; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon. * Fisher's exact test

3.6.3.6 Comparison of RA and age- and sex-matched HS tendon findings on ultrasound

144 patients were selected from the BEACON database with early inflammatory arthritis meeting EULAR/ACR 2010[30] criteria for RA. This comparison cohort of RA patients were all matched with 144 out of the 939 HS by gender and age (within 2 years), and also where possible smoking status (116/144). As expected the prevalence of TSH and TPD grade ≥1 in RA patients was much higher compared to HS, particularly with much higher prevalence of grade 2 and grade 3 findings (Table 3-43).

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
TSH			
DF 1	10 (3.5)	5 (1.8)	0 (0.0)
DF 2	21 (7.3)	28 (9.7)	1 (0.4)
DF 3	29 (10.1)	17 (5.9)	4 (1.4)
DF 4	18 (6.3)	10 (3.5)	0 (0.0)
DF 5	22 (7.6)	13 (4.5)	1 (0.4)
ECU	27 (9.4)	32 (11.2)	6 (2.1)
TPD			
DF 1	6 (2.1)	4 (1.4)	0 (0.0)
DF 2	17 (5.9)	15 (5.3)	4 (1.4)
DF 3	19 (6.6)	19 (6.6)	2 (0.7)
DF 4	10 (3.5)	10 (3.5)	0 (0.0)
DF 5	12 (4.2)	11 (3.9)	0 (0.0)
ECU	18 (6.3)	37 (12.9)	7 (2.5)

Table 3-43 Ultrasound findings in patients with Rheumatoid Arthritis

TSH, tenosynovial hypertrophy; TPD, power Doppler within tendon sheath; TEF, tenosynovial effusion; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon

There were significantly more TSH and TPD grade ≥ 1 detected in RA patients compared to age and sex-matched HS (Table 3-44). Tenosynovitis as defined by TSH and power Doppler grade ≥1 in DF and ECU tendons was more prevalent in RA patients (52.8%) compared to HS (0.9%).

	HS tendons grade ≥1 Number (%)	RA tendons grade ≥1 Number (%)	p value* HS vs RA (age and sex matched)
Total number of tendons at each level	288	288	
DF 1 TSH grade ≥1 n (%)	0 (0)	15 (5.2)	< 0.001
DF 2 TSH grade ≥1 n (%)	0 (0)	50 (17.4)	< 0.001
DF 3 TSH grade ≥1 n (%)	1 (0.3)	50 (17.4)	< 0.001
DF 4 TSH grade ≥1 n (%)	1 (0.3)	28 (9.7)	< 0.001
DF 5 TSH grade ≥1 n (%)	5 (1,7)	36 (12.5)	< 0.001
ECU TSH grade ≥1 n (%)	6 (2.1)	60 (20.1)	< 0.001
DF 1 TPD grade ≥1 n (%)	0 (0)	10 (3.5)	0.002
DF 2 TPD grade ≥1 n (%)	0 (0)	36 (12.5)	< 0.001
DF 3 TPD grade ≥1 n (%)	0 (0)	40 (13.9)	< 0.001
DF 4 TPD grade ≥1 n (%)	0(0)	20 (6.9)	< 0.001
DF 5 TPD grade ≥1 n (%)	0 (0)	23 (8.0)	< 0.001
ECU TPD grade ≥1 n (%)	0 (0)	58 (20.3)	< 0.001

Table 3-44 Ultrasound tendon findings in age- and sex-matched healthy subjects and patients with RA

HS, healthy subject; THS, tenosynovial hypertrophy; TPD, power Doppler within the tendon sheath; TEF, tenosynovial effusion; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon. * Fisher's exact test.

3.6.3.7 Comparison of RA patients with whole cohort of healthy subjects

The graphs in Figure 3-21 illustrate the low proportions of TSH and TPD TSH and TPD grade ≥1 in HS across the age groups in stark contrast to the prevalence of tenosynovitis in the comparison cohort of patients with RA. Prevalence of TEF in the HS was also low at less than 5% across the age groups. Unfortunately there were no TEF ultrasound data amongst the RA cohort to compare against because TEF was not routinely recorded as part of the BEACON scanning protocol at the time the scans were performed.

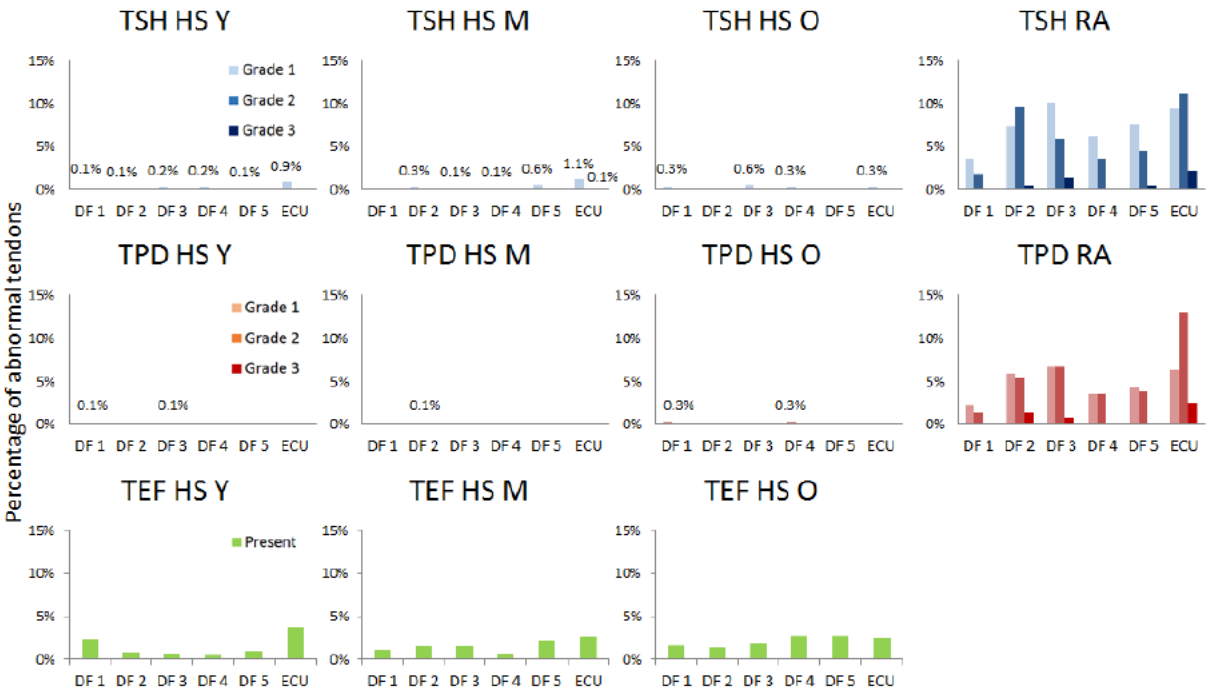

Figure 3-21 Percentage of tendons with grade ≥ 1 tenosynovial hypertrophy, tendon sheath power Doppler and tenosynovial effusion in digit flexor tendons 1-5 and extensor carpi ulnaris tendons for healthy subjects by age groups and Rheumatoid Arthritis patients.

TSH and TPD quantified as grades 0 -3, with grade 0 being absent; TEF measured only in HS, and as either present or absent.
HS Y, 18-39 years; HS M, 40-59 years; HS O, 60-80 years.
HS, healthy subjects; RA, Rheumatoid Arthritis patients; TSH, tenosynovial hypertrophy; TPD, Power Doppler within tendon sheath; TEF, tenosynovial effusion; DF, digit flexor tendons; ECU, extensor carpi ulnaris tendons

The majority (791/939, 84.2%) of HS had a complete absence of tendon abnormalities, with grade 0 for TSH, TPD and TEF in all DF 1-5 and ECU tendons. There were low levels of tenosynovial power Doppler present with 99% (931/939) of HS having grade 0 TPD in all tendons scanned (Table 3-45).

	TSH all grade 0 n (%)	**TPD all grade 0 n (%)**	**TEF all grade 0 n (%)**	**TSH, TPD and TEF all grade 0 n (%)**
Healthy subjects n= 939	907 (96.6)	931 (99.1)	808 (86.0)	791 (84.3)
RA patients n= 144	68 (47.2)	81 (56.3)	n/a	n/a

Table 3-45 Healthy subjects and Rheumatoid arthritis patients with grade 0 for ultrasound findings

HS, healthy subjects; RA, patients with Rheumatoid Arthritis; TSH, tenosynovial hypertrophy; TPD, power Doppler within tendon sheath; TEF, tenosynovial effusion

3.6.4 Summary

In this large study of selected tendons in hands and wrists of healthy subjects, the aim was to determine the extent of tendon abnormalities compatible with ultrasound detected inflammation in HS. In particular, the focus was to examine a broad age range of HS encompassing the age of incidence of RA.

There was low prevalence of grade ≥ 1 tenosynovial hypertrophy and Power Doppler within the tendon sheath in all DF and ECU tendons across the age range. The few abnormalities observed were almost exclusively grade 1 in severity. In contrast the cohort of patients with a recent diagnosis of RA had significantly more grade ≥ 1 TSH and TPD. This highlights that even older healthy subjects are very unlikely to have grade ≥ 1 TSH or TPD in the DF or ECU tendons, so any positive ultrasound findings could be regarded as significant in the right clinical context.

This data should help the decision making of health care professionals performing ultrasound in early arthritis or disease management clinics. They should feel confident in interpreting mild TSH and TPD in digit flexor of extensor carpi ulnaris tendons as significant in patients of all ages presenting with possible early inflammatory arthritis. Digit flexor and ECU tendons can be easily examined during routine ultrasound examination so could be included in abbreviated scanning protocols.

3.7 Chapter 3 Discussion

This international study of over 900 HS is currently the largest cohort of healthy subjects with ultrasound of selected joints and tendons in hands, wrists and feet. The number of HS recruited has given the study sufficient power to produce some interesting and statistically significant results. The older age range is also well represented with 549/954 (57.5%) in the 40-80 years range, providing a large cohort of HS that can be used as comparison for patients with inflammatory arthritis and encompassing the typical age range for patients presenting with Rheumatoid arthritis.[161] The mean age of 44.4 years (±15.5) is higher than the previous largest study of HS.[165]

Examination of the joint data revealed significantly more SH grade ≥ 1 in the HS O age group in MCP 2, 3 and 4, PIPJ 1-3, the wrist and MTPJ 1 ($p<0.001$) confirming the hypothesis of an age-related effect on incidence of low grade ultrasound findings in joints. Looking at prevalence ≥ 5% of SH, PD and EF grade ≥ 1 in each of the three age groups (HS Y, 18-39 years; HS M, 40-59 years; HS O, 60-80 years) we have been able to propose cut off grades for what might be expected to be "normal" on MSUS in healthy subjects in each of these age ranges (see section 3.3.10). Previous ultrasound studies have not had sufficient power to draw these age-related conclusions. [165] [178]

There was high prevalence of SH grade ≥ 1 MTPJ 2-4 and a significant age-related effect was not seen at MTPJ 2, 3 and 5. Binomial regression analysis with correction for age, gender, smoking and manual occupation showed BMI was significantly associated with SH grade ≥ 1 in MTPJ 3-5. This knowledge could help Rheumatology sonographers when examining the MTPJs, because SH grade ≥ 1 might be considered normal for the patient's BMI, and only presence of PD grade ≥ 1 would provide evidence of active synovitis. One study has examined

the effect of obesity and correlation of swollen joints detected on clinical examination with ultrasound evidence of synovitis in RA patients,[214] but this examined the joints included in the DAS-28 and did not look at MTPJs. Furthermore this study used SH grade ≥2 and/or PD grade ≥1 on ultrasound as evidence of synovitis. The biomechanics of RA versus a healthy populations is likely to be different, therefore our findings should be regarded as novel.

The prevalence of SH grade ≥ 1 in MTPJ 5 was low at less than 5% across the age range; this could help sonographers to identify that positive ultrasound SH findings in MTPJ 5 might be abnormal as they are not often seen even in the older age range. This is helpful because MTPJ 5 is often affected in RA, with the detection of erosions in this joint helping to predict which patients with ACPA positivity may go on to develop RA.[215] The detection of SH before erosions develop may therefore also help with prediction of development or diagnosis of RA. No grade 3 SH was seen in MTPJ 5 in HS in the younger age group (18-39 years old), so this should be regarded as pathological if detected on MSUS.

Power Doppler grade ≥1 was rarely seen in any of the scanned joints at <5% across the age range. It was significantly more prevalent in the older age groups in MCPJ 2, 3, wrists and MTPJ 1, but this prevalence was still low, and PD grade ≥1 was particularly rarely seen in the PIPJs. This low PD prevalence means when it is seen on MSUS in the correct clinical context it may represent joint pathology. Studies have shown the utility of PD grade ≥1 in combination with the presence of ACPA positivity in predicting the prognosis of RA.[216 217]

Grade ≥1 joint effusion was much more common than SH and PD in HS across the age range. In particular EF grade ≥1 in MTPJ 1 and PIPJ 1 was found even in young HS. Joint effusion

has been found to be common in the MTPJ of HS in other studies on MRI[218] and MSUS.[165] Our study confirms this and suggests effusion should not be regarded as in any way pathological.

The prevalence of detected erosions in this study was very low in MCPJ 2, 5 and MTPJ 5 at <1% in all groups except in MCPJ 2 in the HS O it was 1.9%. Other studies have suggested a higher prevalence of erosions; a review of MRI of small joints in healthy subjects found that 33% had low grade erosions in MCPJs on MRI.[219] MRI is more sensitive than US in detecting erosions. Also MSUS can only examine structures directly beneath the transducer, so erosions in MCPJ 3-4 especially might be easily missed. In the previous largest ultrasound study of healthy subjects[165] only 4 erosions were found in 207 HS and these were all in MTPJ 1, which were not scanned for erosions in our study.

When examining joint symmetry, left and right joints appeared to have the same distribution of abnormalities from the graphs in Figure 3-3. The tables in 3-6 to 3-9 showed some differences between left and right sides, with low level significant difference in SH grade ≥1 in the right side for MCPJ 2 and MTPJ 1 ($p<0.05$). Other studies[166 171] have found no difference between dominant and non-dominant sides. A study of dentists and teachers showed more grade ≥2 MSUS osteophytes detected in the non-dominant hand of teachers, but more severe grades of osteophytes in the dominant hand of dentists implying a protective effect of activity but an association of repeated joint overload with severe OA.[220] In this study grade ≥1 Os was more prevalent in the dominant side of MTPJ 1 only ($p<0.05$), and the number of manual workers were too small to compare dominant sides and MSUS findings.

The demographics of the recruited HS had a similar proportion of females to patients with RA. This was unintentional, but does help to better compare HS with RA patients. The larger

proportion of females in this study may reflect the healthcare setting that many HS were recruited from, which was likely due to ease of access of these individuals. It also may reflect that more women are happy to volunteer. The older HS recruited in Birmingham were accessed from a volunteer cohort of elderly healthy subjects, which had similar proportions of females and males. These recruitment locations may have introduced bias, meaning the HS in this study are not representative of the wider population.

When the tendon findings in RA patients were compared to a group of age- and sex-matched HS the mean BMI of the HS was significantly lower ($p<0.001$) and there were significantly more individuals who had never smoked amongst the HS ($p<0.05$). Smoking is known to be a risk factor for RA so there is a higher prevalence in these patients compared to the general population.[221] This may have affected the comparison of ultrasound results in HS and RA patients. The positive tendon findings were too low in this study to test binomial regression analysis, although when examining the joint ultrasound data in this study history of smoking amongst HS (when corrected for age, sex, BMI and manual occupation) was only significantly associated with prevalence of SH grade ≥1 in PIPJ 1 and MTPJ 1 ($p<0.05$). BMI, after correction, was significantly associated with positive SH findings in MTPJ 3-5, which may be due to the mechanical effect of weight loading through these joints.

Examining potential confounders, we found significantly more grade ≥1 SH in MCP 2-4 ($p\leq0.001$), and PIPJ 1 and MTPJ 5 ($p<0.05$) in the HS currently working in or retired from manual occupations, with significance remaining in MCP2-4 when age, sex, smoking and BMI were corrected in binomial logistic regression analysis. This may be due to more repetitive, mechanical loads through these joints in manual occupations. However, occupations were not recorded in the same way in all centres and on reflection it may have been helpful to specify

main occupation if retired, and how many years HS had been in work. A standardised list of occupation groups such as the Standard Occupational Classification SOC 2010 may have also improved consistency in recording this information. The Office of National Statistics states 16% of workers in the UK in 2018 were in manual occupations (skilled trade or process, plant and machine operatives);[222] therefore 153/954 HS in this study should have been in manual occupations to be representative of the UK working population instead of the actual number 75/954.

The examination of grade ≥1 abnormalities on ultrasound against the regular physical hobbies and activities reported by healthy subjects showed more prevalent SH positive US findings in those who were not practising hobbies involving high impact on upper or lower limbs. This is contrary to what might be expected, but may have been confounded by the group not involved in high intensity/impact sports being older. There were more EF grade ≥1 in those partaking in high impact sports which is likely physiological. Although there is a lack of large healthy control studies looking at the effect of high impact sports on joint effusion, small studies have shown more joint effusions in athletes.[223] There was no formal recording of how frequently HS practised their hobbies, for how many years and whether these activities were past or current. Also, a standardised method of deciding which activities have a high impact on upper or lower limbs should have been decided before data collection began.

In this study we did not examine the potential relationship of ultrasound-detected presence of grade ≥1 osteophytes with the presence of grade ≥1 synovial hypertrophy with or without grade ≥1 power Doppler. In future analysis it would be interesting to examine this, and if there is a significant correlation then is this independent of age of healthy subject?

A variety of different ultrasound machines and probes were used in the 23 recruiting centres (detailed in Table 3-3) and there were many different contributors to the ultrasound data raising the issue of reliability. These were all experienced OMERACT centres which have collaborated on many ultrasound projects previously, and were involved in the consensus decision on the new OMERACT grading system. However, as the reliability section illustrated many centres did not grade MTPJ and wrist joints in the same way. The anomalies in SH across the centres were first examined according to age distribution of the HS scanned, however this did not explain the differences. The pilot central regrading exercise revealed many inconsistencies in grading of SH in these joints and led to the decision to centrally regrade all ultrasound images.

The first step in centrally regrading all images was to agree with all the collaborators involved in the study on how images would be regraded. It was a sensitive issue to broach, with many of the contributing sonographers being highly experienced, and there was initially some reluctance from some collaborators to question the gradings that were submitted. Reliability had initially been addressed by the first HS recruited in each centre being centrally regraded. However, given the inter-centres variation in the results a more comprehensive grading exercise before data collection may have avoided the need for centrally regrading images. The MTPJ and wrist joint atlases produced contain more images than the currently available grading atlases references for theses joints[212] so should help Rheumatology sonographers grade consistently and will support the already published OMERACT consensus grading system.

The ultrasound data on tendons was much more consistent between centres compared to the joint data, so further presentation and publication was possible without the need to centrally regrade these images. Previously, the prevalence of sonographic tenosynovial abnormalities in healthy subjects across the age range was not well documented in the available literature, with

less than 50 healthy controls in most studies.[172 224 175] With over 900 HS in this study there were sufficient numbers to draw some significant conclusions.

There were remarkably low proportions of grade ≥ 1 tenosynovial hypertrophy (TSH), power Doppler (TPD) and tenosynovial effusion (TEF) across the age range in HS. TEF was more prevalent than TSH or TPD in HS but these proportion were still low. Although MRI studies have suggested tenosynovial effusion to be almost ubiquitous in digit flexor tendons in HS[225], we have shown that ultrasound detects smaller numbers, with less than 2% of digit flexor tendons having effusion even in the older age group. This may be due to the two dimensional nature of scanning tendons with ultrasound, and higher sensitivity of MRI.

This study shows in a large cohort that tenosynovial abnormalities on ultrasound are significantly more prevalent in early RA compared to age- and sex-matched HS, similar to a smaller previous study.[150] However, the HS had a significantly lower BMI and were less likely to have ever smoked compared to the RA cohort. These differences may have confounded results, but it is unlikely because the prevalence of tendon abnormalities in RA patients was strikingly higher.

There is an issue of real world application of this data because HS were very healthy compared to the normal population in with exclusions of individuals with joint pain, overt osteoarthritis and a number of other health conditions. This means this HS cohort may have fewer tendon abnormalities than an unselected general population of 60-80 year olds seen in a real world clinic. However, the design of this study was to document what is normal in healthy subjects without confounding factors such as osteoarthritis or the possibility of early undiagnosed inflammatory arthritis being present and skewing the healthy subject data.

Future work

At the time of submitting this thesis the joint ultrasound data central regrading has not yet been completed. Once this has occurred, the joint data will be re-analysed using the same methodology as in this thesis and then published alongside the study protocol and the wrist and MTPJ atlases.

4 ULTRASOUND FINDINGS IN PATIENTS WITH CLINICALLY SUSPECT ARTHRALGIA

4.1 Introduction

Rheumatoid arthritis (RA) may initially present with a variety of symptoms and signs before it fully evolves into a clinical picture fulfilling classification criteria.[153] Clinically suspect arthralgia (CSA), or inflammatory arthralgia, is a term used when clinicians believe the joint pain and other symptoms experienced by a patient may represent a prelude to developing RA. In the last few years there has been evidence to recommend that earlier diagnosis of RA with resulting earlier treatment lead to a better prognosis[76] and may even delay progression of CSA to RA.[77] Therefore, identifying which features predict who will go on to develop RA is important.

In 2017 a European League Against Rheumatism (EULAR) consensus group published guidance on recognising which characteristics of patients with CSA are most important in identifying those at risk of progression on to RA (Table 4-1).[143] If ≥3 of these feature are present sensitivity is >90%, and if ≥4 are present specificity is >90% for CSA. However, this study represents a consensus of expert opinion, and these characteristics have not been prospectively tested for their ability to differentiate those at risk of developing RA from those that are not.

Joint symptoms of recent onset (duration <1 year)
Symptoms located in MCP joints
Duration of morning stiffness 60 minutes or more
Most severe symptoms present in the early morning
Presence of a first degree relative with RA
Difficulty with making a fist
Positive squeeze test of MCP joints

Table 4-1 European League against rheumatism (EULAR) consensus agreed features of clinically suspect arthralgia

MCP, metacarpophalangeal; RA, Rheumatoid arthritis

There is evidence that presence of anti-citrullinated peptide antibodies (ACPA) may help to predict which patients go on to develop RA, even in patients with non-specific musculoskeletal symptoms.[226] The use of musculoskeletal imaging has also been used as a predictive tool. Inflammatory MRI changes seen in patients with CSA, as well as older age, a positive ACPA, higher body mass index (BMI), higher erythrocyte sedimentation rate (ESR) and a lower tender joint count were associated with development of RA in the Leiden cohort.[156] An MRI without signs of joint or tendon inflammation in patients with CSA may predict those who do not go on to develop RA after 1 year.[157]

Musculoskeletal ultrasound (MSUS) is another imaging modality that has predictive value for patients with CSA. One study of CSA patients found that progression to RA was associated with: positive Rheumatoid factor (RF), positive ACPA; early morning stiffness lasting more than 30 minutes; and ultrasound detected synovitis.[158] Another study suggested an ultrasound negative for inflammation had an 89% negative predictive value for the development of RA by 12 month follow up. [158]

The study reported herein reports on clinical and ultrasound data in CSA patients available from the Birmingham Early Arthritis Cohort (BEACON). The primary aim was to characterise the presenting ultrasound features of patients with CSA, particularly by looking at a larger range of joints than other studies.[146] The secondary aim was to assess whether any of these ultrasound findings or patient characteristics are associated with progression from CSA to IA or RA. A 24-month cut-off for the development of clinical inflammatory arthritis was chosen, which is a longer time period than other some studies[143 158 159 227] as it may help to further define the utility of ultrasound in prediction of development of RA.

4.2 Hypothesis

The presence of clinical and ultrasound features of patients presenting with clinically suspect arthralgia (CSA) may help to predict those patients that will go on to develop clinically evident inflammatory arthritis.

4.3 Objective

A retrospective study of CSA patients with 24 month follow up data.

4.4 Methods

4.4.1 Data collection

The Birmingham Early Arthritis Cohort (BEACON) databases maintained by the Rheumatology research departments at City and Queen Elizabeth Hospitals Birmingham, United Kingdom, were searched from April 2014 to April 2019. Databases were filtered to find patients with a baseline diagnosis of clinically suspect arthralgia or inflammatory arthralgia, judged by individual decision-making clinicians at baseline clinic visit. Those patients who had been consented to BEACON at least 24 months previously were selected, aiming for the availability of 24-month classification outcome data. Patients enrolled onto BEACON have six monthly research appointments, with a clinician review at 24-months to give an outcome diagnosis if patients meet fulfilment of classification criteria for conditions such as RA,[153] CSA,[143] psoriatic arthritis,[228] axial or peripheral spondyloarthritis,[229] or systemic lupus erythematosus.[230]

The BEACON databases include electronic copies of the information from clinical research forms (CRFs) collected at the time of the patient BEACON research visits. Hard copies of the CRFs were checked if any data were missing (an example CRF can be found in Appendix 4).

Additional data were also collected from electronic patient records to search for the EULAR consensus criteria (see Table 4-1) if it was not already included in the database. Table 4-2 shows the inclusion and exclusion criteria.

Inclusion criteria
Patients with baseline diagnosis of inflammatory arthralgia or CSA in the BEACON database
Exclusion criteria:
No baseline ultrasound
No 24 month follow up diagnosis
Unknown sonographer

Table 4-2 Inclusion and exclusion criteria

CSA, clinically suspect arthralgia; BEACON, Birmingham Early Arthritis Cohort

4.4.2 Ultrasound

Patients recruited to the BEACON cohort routinely undergo baseline ultrasound of selected joints and tendons in hands, wrists and feet. In the Queen Elizabeth Hospital, the ultrasound machine used was a Logiq E9, and in Birmingham City Hospital it was a Logiq S8. Liberal amounts of gel were used to avoid excessive compression of structures examined. All joints and tendons were scanned with either an 8-18 MHz hockey stick probe or a 6-15 MHz linear probe. Standard BEACON joint specific pre-set parameters were used to optimise imaging for greyscale and power Doppler, which were centrally calibrated on both machines. A multi-planar greyscale and power Doppler ultrasound examination of bilateral joint and tendon sites was performed in a systematic fashion (see Table 4-2), with views recorded according to EULAR standard reference scan guidelines.[188]

Metacarpophalangeal joints (MCPJ) 1-5
Proximal interphalangeal joints (PIPJ) 1-5
Wrists (radio-, inter- and ulnar-carpal views)
Metatarsophalangeal joints (MTPJ) 2-5[#]
Digit flexor (DF) tendons at MCPJs 1-5*
Extensor carpi ulnaris (ECU) tendon*

Table 4-3 List of joints and tendons scanned by ultrasound

*DF and ECU tendons not scanned as routine practice prior to September 2015

[#]MTPJ 1 was not scanned as part of the protocol because ultrasound frequently detects SH and PD in this joint even in healthy subjects[165]

The joints and tendons in Table 4-2 were graded between 0 and 3 for the presence of synovial hypertrophy (SH) and Power Doppler (PD), with grade 0 representing an absence of the ultrasound parameter and grade 3 representing most severe disease. These baseline ultrasound assessments were recorded on an ultrasound proforma at the time of the ultrasound scan. These ultrasound data were then transferred from paper copy to electronic database. These baseline scans had been performed by one of four blinded Rheumatology sonographers, in a temperature-controlled radiology suite. Scans were excluded if images were not available for reliability studies. Reliability studies were carried out by a blinded assessor using 10% of scanned images from the two sonographers included in this study. The mean kappa coefficient for synovial hypertrophy and power Doppler for sonographer 1 was 0.62 and for sonographer 2 it was 0.55.

4.4.3 Statistics

All statistical analysis was carried out using IBM SPSS Statistics version 26. Binary variables such as gender, rheumatoid factor or anti-CCP positivity and positive MCP squeeze test, was assessed using Fisher's exact test. Continuous variables such as age and BMI were not normally distributed; significance was therefore assessed using the non-parametric Kruskall-Wallis test. The joint and tendon gradings were dichotomised into either present (grade 1-3) or absent (grade 0). Fisher's exact test was used to compare the proportions of grade 1 to 3 SH or PD

between patients with and without inflammatory arthritis, or with RA or another IA, at 24-month diagnosis.

4.5 Results

Initially 155 patients were extracted, but after exclusions (see Figure 4-1) there were 43 patients with CSA at baseline diagnosis included in this study that had ultrasound data and 24 month follow up. Unfortunately, of the patients that did not have a 24 month diagnosis, 60% (21/35) had their 24 month BEACON visit delayed due to the COVID-19 pandemic.

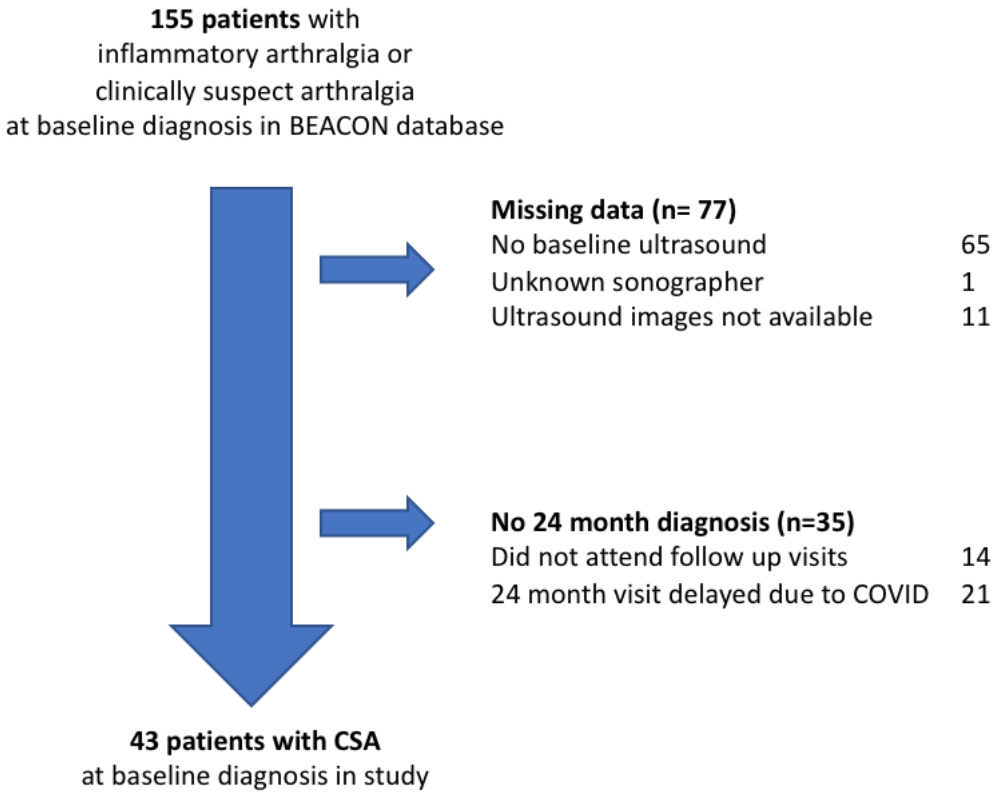

Figure 4-1 Consort diagram of exclusions
CSA, clinically suspect arthralgia; COVID, coronavirus pandemic

4.5.1 Baseline Clinically Suspect Arthralgia Demographics

The 78 patients with CSA at baseline diagnosis that also had ultrasound data available were analysed (43 with 24 month outcome, 35 without). Most patients were recruited before the EULAR CSA consensus criteria were published[143] therefore many of these items were not specifically included on the clinical research proforma because they were not previously considered important in the diagnosis of CSA. The diurnal variation in symptoms and ability to make a fist were not recorded in most cases (83.8% and 79.5% respectively). As MCP squeeze test was again only included after a certain time point, tender MCP joints on examination was used as a surrogate for positive MCP squeeze test. Appraisal of these patients against the EULAR consensus criteria for CSA revealed 56.4% (44/78) met three or more of these criteria which is thought to be >90% sensitive for CSA, and 38.5% (30/78) patients met 4 or more which is > 90% specific for CSA.[143]

	All baseline CSA patient data	CSA patients with 24 month data	CSA patients with no 24 month data	p value 24M vs no 24M
n	78	43	35	
Age, years, median (IQR)	44.0 (33.8, 52.3)	45.0 (35.0, 56.0)	43.0 (33.0, 49.0)	0.252
BMI, median (IQR)	28.1 (23.8, 31.3)	29.0 (26.3, 33.0)	26.6 (21.6, 29.4)	0.046
Female, n (%)	58 (72.5)	30 (69.8)	28 (80.0)	0.435
Ethnicity, n (%)	Asian 15 (18.8), Black 5 (6.3), Caucasian 52 (65.0), Mixed 4 (4 (5.0) NA 2 (2.5)	Asian 6 (14.0), Black 3 (7.0), Caucasian 30 (69.8), Mixed 3 (7.0)	Asian 9 (25.7), Black 2 (5.7), Caucasian 22 (62.9), Mixed 1 (2.9)	0.72
Smoking, n (%)	Current 14 (17.5), Ever 64 (80.0), Never 40 (50.0)	Current 6 (14.0), Ever 37 (80.0), Never 21 (48.8)	Current 8 (22.9), Ever 27 (77.2), Never 19 (54.3)	0.349
Symptom duration before diagnosis, wk median (IQR)	35.9 (17.9, 78.3)	47.0 (18.0, 161.0)	27.0 (17.0, 52.4)	0.067
< 1yr symptoms, n (%)	48 (60)	23 (53.5)	25 (52.1)	0.160
Duration of EMS at baseline, mins median (IQR)	60 (5, 120)	90 (15, 120)	60 (0, 60)	0.027
EMS ≥ 60 mins, n (%)	62 (77.5)	34 (79.1)	28 (80.0)	1.000
Symptoms in MCPs, n (%)	51 (63.8)	34 (78.9)	17 (34.0)	0.035
First degree relative RA, n (%)	17 (21.3)	7 (16.3)	10 (28.6)	0.271
Tender MCPs, n (%)	40 (50.0)	28 (65.1)	12 (34.3)	0.09
Acute mode of onset, n (%)	24 (30.0)	11 (25.6)	13 (37.1)	0.012
Psoriasis history, n (%)	2 (2.5)	2 (4.7)	0 (0.0)	0.337
RF positive, n (%)	26 (32.5)	16 (37.2)	10 (28.6)	0.129
ACPA positive, n (%)	23 (28.7)	12 (27.9)	11 (31.4)	0.805
ESR, median (IQR)	13.0 (8.0, 23.8)	15.5 (7.8, 28.3)	12.0 (7.8, 17.8)	0.351
CRP, median (IQR)	4.0 (1.0, 7.0)	3.5 (1.0, 8.3)	4.0 (1.0, 7.0)	0.685
Assessor global VAS, median (IQR)	10 (5, 19)	13 (6, 19)	8 (9, 16)	0.299
Patient global VAS, median (IQR)	47 (8, 59)	47 (23, 63)	22 (5, 58)	0.126
Patient pain VAS, median (IQR)	47 (22, 70)	54 (31, 74)	38 (20, 61)	0.037
EMS patient VAS, median (IQR)	55 (26, 82)	69 (38, 83)	44 (13, 79)	0.092
Fatigue severity VAS, median (IQR)	65 (28, 82)	69 (43, 86)	60 (15, 76)	0.067
TJC 68, median (IQR)	6 (3, 18)	6 (4, 19)	6 (1, 15)	0.185
TJC 28, median (IQR)	4 (1, 9)	4 (2, 11)	3 (0, 8)	0.170

Table 4-4 Demographics and clinical data of patients with clinically suspect arthralgia at baseline diagnosis

CSA, clinically suspect arthralgia arthritis; M, months; wk, weeks; mins, minutes; IQR, interquartile range; BMI, body mass index; CRP, C reactive protein; ESR, estimated sedimentation rate; VAS, visual analogue score; EMS, early morning stiffness; TJC, tender joint count; NA, not applicable

The baseline data were compared between CSA patients who had baseline data alone with patients who had 24 month outcome data. There were no significant differences in RF, ACPA, CRP or ESR between the group with 24 month follow up and the group without. More CSA patients with 24 month follow up had reported symptoms in their MCP joints at baseline assessment ($p = 0.035$) and there was also longer duration of EMS in in this group ($p=0.027$) although there was no difference in the number of CSA patients that had ≥ 60 minutes of EMS.

4.5.2 Diagnosis at 24 months

There were 22/43 patients with inflammatory arthritis (IA) at 24 months; 15 of these patients had RA and 7 had another form of inflammatory arthritis (see Table 4-5). There were 21 patients who had not developed IA by 24 month follow up, some of these patients had diagnoses such as osteoarthritis, fibromyalgia and hypermobility.

Diagnosis at 24 months		**n**
Rheumatoid arthritis		15
Other inflammatory arthritis		
Psoriatic arthritis		1
Peripheral spondyloarthritis		1
Unclassified inflammatory arthritis		1
Palindromic rheumatism		1
Gout		1
Polymyalgia rheumatica		1
Undifferentiated connective tissue disease		1
	Total	7
Not inflammatory arthritis		21

Table 4-5 Diagnosis at 24 months of patients who had clinically suspect arthralgia at baseline

4.5.3 Demographics of patients with and without inflammatory arthritis at 24 months

The 43 patients were split in to two groups to compare those who had a diagnosis of inflammatory arthritis at their 24 month BEACON visit (which included patients who had RA), and those who did not have inflammatory arthritis 24 months after baseline BEACON visit. There were no significant differences in age, sex, BMI, ethnicity of smoking history between these two groups (Table 4-6). Baseline assessments of global health, pain and fatigue visual analogues scores, joints counts and inflammatory markers were not significantly different, although the sample sizes were small.

	IA at 24 months	Not IA at 24 months	p value
n	22	21	
Age, years, median (IQR)	47 (41.5, 53.8)	43 (33.5, 57.5)	0.752
BMI, median (IQR)	29.8 (26.6, 33.3)	28.1 (25.4, 33.2)	0.532
Female, n (%)	18 (81.8)	12 (57.1)	0.104
Ethnicity, n (%)	Caucasian 14 (63.6) Asian 5 (22.7) Mixed 2 (9.1) Black 1 (4.5)	White British 16 (76.2) Black 2 (9.5) Asian 1 (4.5) Mixed 1 (4.5) NA 1 (4.5)	
Never smoked, n (%)	12 (54.5)	9 (42.9)	0.305
Duration of symptoms before diagnosis, median (IQR)	54 (22.5,161)	33 (16.5, 292.5)	0.269
< 1yr symptoms, n (%)	8 (36.4)	15 (71.4)	0.033
Duration of EMS at baseline, median (IQR)	60 (5, 120)	120 (60, 120)	0.267
EMS ≥ 60 mins, n (%)	13 (50.9)	17 (81.0)	0.185
Symptoms in MCPs, n (%)	15 (68.2)	19 (90.5)	0.225
First degree relative RA, n (%)	3 (13.6)	7 (33.3)	0.216
Tender MCPs, n (%)	11 (50.0)	17 (81.0)	0.055
Acute mode of onset, n (%)	5 (22.7)	6 (28.6)	0.796
Psoriasis history, n (%)	2 (9.1)	0 (0.0)	0.488
RF positive, n (%)	13 (59.1)	3 (14.3)	0.004
ACPA positive, n (%)	11 (50.0)	1 (4.8)	0.002
ESR, median (IQR)	16 (9,30.5)	9 (7, 22.5)	0.178
CRP, median (IQR)	4 (2, 8.8)	3 (1, 8.5)	0.355
Patients taking DMARDs at 24 months, n (%)	15 (68.2)	5 (23.8)	<0.001
Assessor global VAS, median (IQR)	10.5 (5, 20.5)	13 (6, 18)	0.990
Patient global VAS, median (IQR)	50 (30.3, 78.3)	43 (11.8, 50.0)	0.084
Patient pain VAS, median (IQR)	62.5 (28, 79)	47.5 (32,8, 72.5)	0.450
EMS patient VAS, median (IQR)	69 (52, 89.5)	69.5 (28.3, 77.3)	0.201
Fatigue severity VAS, median (IQR)	68.5 (43.3, 85.0)	72 (37.8, 89.8)	0.762
TJC 68, median (IQR)	6 (3.75, 18,25)	7 (4, 22)	0.742
TJC 28, median (IQR)	2.5 (1, 8)	5 (3, 13.5)	0.081

Table 4-6 Baseline demographics and clinical data of patients with and without inflammatory arthritis at 24 months

IA, inflammatory arthritis; IQR, interquartile range; BMI, body mass index; RF, Rheumatoid factor; ACPA, anti-citrullinated peptide antibody; CRP, C reactive protein; ESR, estimated sedimentation rate; DAS, disease activity score; EMS, early morning stiffness; TJC, tender joint count; VAS, visual analogue score; NA, not applicable

The seven EULAR CSA consensus criteria[143] were compared between those with and without inflammatory arthritis 24 months after baseline diagnosis of CSA. There were significantly

more patients with less than one year of inflammatory arthralgia symptoms before their diagnosis of CSA in the group that did not go on the develop IA by 24 months (p=0.033). This is contrary to what would be expected from the consensus criteria. Similarly, there was a higher proportion of CSA patients in the non-IA group at 24 months with tender MCP joints at baseline clinical assessment (which implies they would have had a positive MCP squeeze test) which was approaching significance (p=0.055); this is contrary to what might be expected according to the EULAR consensus criteria for CSA.

RA related autoantibodies were associated with the development of an inflammatory arthritis in CSA patients by 24-months of follow up. Rheumatoid factor and ACPA positivity were significantly more prevalent in the group with inflammatory arthritis at 24-months (p=0.004, p=0.002 respectively).

Unsurprisingly, patients with IA at 24-months were significantly more likely to be on a DMARD by this time point (p<0.001). There were five patients in the non-IA at 24-month group on a DMARD; all of them had a 24-month diagnosis of CSA. One of these CSA patients was on methotrexate and the other four were taking Hydroxychloroquine (see Table 4-7). All of these DMARDs were started within 12 months of CSA diagnosis.

	CSA patient 1	CSA patient 2	CSA patient 3	CSA patient 4	CSA patient 5
24 month DMARD	HCQ	MTX	HCQ	HCQ	HCQ
Age, years	58	78	32	41	66
Gender	Male	Male	Female	Male	Male
BMI	23	31.1	38.9	28.1	32.9
Ethnicity	White British	White British	British Asian - Pakistani	White Irish	White British
Smoking status	Never	Ex	Never	Ex	Ex
Duration of symptoms, weeks	33.0	5	15	261	16
Symptoms located in MCPJs?	no	yes	yes	yes	yes
Duration of EMS, minutes	0	60	180	120	120
FH RA first degree relative	yes	no	no	yes	no
Positive MCPJ squeeze?	negative	tender MCPJs	tender MCPJs	tender MCPJs	tender MCPJs
Mode of onset	Palindromic	Acute	Insidious	Insidious	Insidious
History of psoriasis	Never	Never	Never	Never	Never
Assessor global disease severity VAS	3	50	26	24	18
Patient pain VAS	10	100	47	68	74
Patient global VAS	4	4	47	47	52
Patient fatigue severity VAS	3	80	51	65	80
TJC 68	1	6	9	22	4
TJC 28	1	6	7	15	4
ESR (mm/hr)	2	33	41	19	22
CRP (mg/L)	<3	19.0	14.0	7.0	1.0
RF level (IU/mL)	103	710.0	<11.0	<11.0	<11.0
ACPA level (U/mL)	332	1.2	1.9	1.2	1.2

Table 4-7 Baseline demographics and clinical data of patients with clinically suspect arthralgia and on a DMARD at 24 month follow up

CSA, clinically suspect arthralgia; BMI, body mass index; MCPJ, metacarpophalangeal joint; EMS, early morning stiffness; FH, family history; RA, Rheumatoid Arthritis; VAS, visual analogue score; TJC, tender joint count; ESR, estimated sedimentation rate; CRP, C reactive protein; RF, Rheumatoid factor; ACPA, anti-citrullinated peptide antibody

The case information in Table 4-7 shows that the CSA patient started on Methotrexate was strongly seropositive for RF, and another patient who was on Hydroxychloroquine at baseline visit was strongly positive for ACPA. These patients in particular may have gone on to develop RA if DMARDs were not initiated early.

4.5.4 Ultrasound data on patients with or without inflammatory arthritis at 24 months

The baseline ultrasound scans for CSA patients were compared between those with and without IA at 24-month BEACON appointment (see Table 4-8). The only joints with significantly

different proportions of grade ≥ 1 synovial hypertrophy between these two groups were in MCPJ 2 and MCPJ 3 (p=0.021 and p=0.039 respectively), with the higher prevalence in the group that went on to develop IA.

	IA at 24 months	Not IA at 24 months	IA at 24 months vs not IA at 24 months p value
Total number of joints	**44**	**42**	
MCP1 SH grade ≥1 n (%)	5 (11.4)	1 (2.4)	0.203
MCP2 SH grade ≥1 n (%)	15 (34.1)	5 (11.9)	0.021
MCP3 SH grade ≥1 n (%)	11 (25.0)	3 (7.1)	0.039
MCP4 SH grade ≥1 n (%)	2 (4.5)	2 (4.8)	1.000
MCP5 SH grade ≥1 n (%)	3 (6.8)	0 (0.0)	0.242
PIP1 SH grade ≥1 n (%)	3 (6.8)	1 (2.4)	0.616
PIP2 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
PIP3 SH grade ≥1 n (%)	1 (2.3)	0 (0.0)	1.000
PIP4 SH grade ≥1 n (%)	1 (2.3)	0 (0.0)	1.000
PIP5 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
MTP2 SH grade ≥1 n (%)	14 (31.8)	6 (14.3)	0.074
MTP3 SH grade ≥1 n (%)	7 (15.9)	3 (7.1)	0.315
MTP4 SH grade ≥1 n (%)	4 (9.1)	2 (4.8)	0.677
MTP5 SH grade ≥1 n (%)	3 (6.8)	0 (0.0)	0.242
Wrist RC SH grade ≥1 n (%)	6 (13.6)	5 (11.9)	1.000
Wrist IC SH grade ≥1 n (%)	2 (4.5)	1 (2.4)	1.000
Wrist UC SH grade≥ 1 n (%)	1 (2.3)	4 (9.5)	0.197
Total number of tendons	**30**	**28**	
DF1 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
DF2 SH grade ≥1 n (%)	1 (2.3)	1 (2.4)	1.000
DF3 SH grade ≥1 n (%)	3 (6.8)	1 (2.4)	0.752
DF4 SH grade ≥1 n (%)	2 (4.5)	1 (2.4)	1.000
DF5 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
ECU SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a

Table 4-8 Baseline ultrasound of synovial hypertrophy in joints and tendons in clinically suspect arthralgia patients, with and without inflammatory arthritis at 24-months

IA, inflammatory arthritis; SH, synovial hypertrophy; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; RC, radio-carpal joint; IC, inter-carpal; joint UC, ulnar-carpal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon.

The presence of grade ≥ 1 Power Doppler in joints and tendons scanned in CSA patients were not significantly different between those who went on to develop IA by 24 months and those who did not (Table 4-9). In the five patients who were on DMARDs but without a diagnosis of IA at 24 months, the patient who was on methotrexate had six joints with evidence of synovitis

on ultrasound (SH and PD grade ≥1), and two other patients had one joint each with ultrasound detected synovitis.

	IA at 24 months	Not IA at 24 months	IA vs not IA at 24 months p value
Total number of joints	**44**	**42**	
MCP1 PD G ≥1 n (%)	4 (9.1)	0 (0.0)	0.117
MCP2 PD G ≥1 n (%)	11 (25.0)	5 (11.9)	0.167
MCP3 PD G ≥1 n (%)	8 (18.2)	3 (7.1)	0.197
MCP4 PD G ≥1 n (%)	2 (4.5)	2 (4.8)	1.000
MCP5 PD G ≥1 n (%)	2 (4.5)	0 (0.0)	0.494
PIP1 PD G ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
PIP2 PD G ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
PIP3 PD G ≥1 n (%)	1 (2.3)	0 (0.0)	1.000
PIP4 PD G ≥1 n (%)	1 (2.3)	0 (0.0)	1.000
PIP5 PD G ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
MTP2 PD G ≥1 n (%)	1 (2.3)	1 (2.4)	1.000
MTP3 PD G ≥1 n (%)	1 (2.3)	1 (2.4)	1.000
MTP4 PD G ≥1 n (%)	1 (2.3)	0 (0.0)	1.000
MTP5 PD G ≥1 n (%)	3 (6.8)	0 (0.0)	0.242
Wrist RC PD G ≥1 n (%)	6 (13.6)	3 (7.1)	0.485
Wrist IC PD G ≥1 n (%)	1 (2.3)	1 (2.4)	1.000
Wrist UC PD G ≥1 n (%)	1 (2.3)	3 (7.1)	0.355
Total number of tendons	**30**	**28**	
DF1 PD G ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
DF2 PD G ≥1 n (%)	0 (0.0)	1 (2.4)	0.907
DF3 PD G ≥1 n (%)	0 (0.0)	1 (2.4)	0.907
DF4 PD G ≥1 n (%)	0 (0.0)	1 (2.4)	0.907
DF5 PD G ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
ECU PD G ≥1 n (%)	0 (0.0)	0 (0.0)	n/a

Table 4-9 Baseline ultrasound of Power Doppler joints and tendons in clinically suspect arthralgia patients, with and without inflammatory arthritis at 24-months

IA, inflammatory arthritis; PD, Power Doppler; G, grade; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; RC, radio-carpal joint; IC, inter-carpal; joint UC, ulnar-carpal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon.

The prevalence of grade ≥1 SH was similar to that of grade ≥ 1 PD, except for in MTPJ 2 in which SH grade ≥1 was much more common (31.8% SH vs 2.3% PD in the IA group, and 14.3% SH vs 2.4% PD in the non-IA group). The individual grades 1-3 for SH and PD can be seen in Figures 4-3 and 4-4. The majority of grade ≥1 SH and PD was of grade 1 severity. The

fewest grade ≥1 SH findings in either group were seen in the PIP joints and tendons, although seven CSA patients had no tendons scanned at baseline.

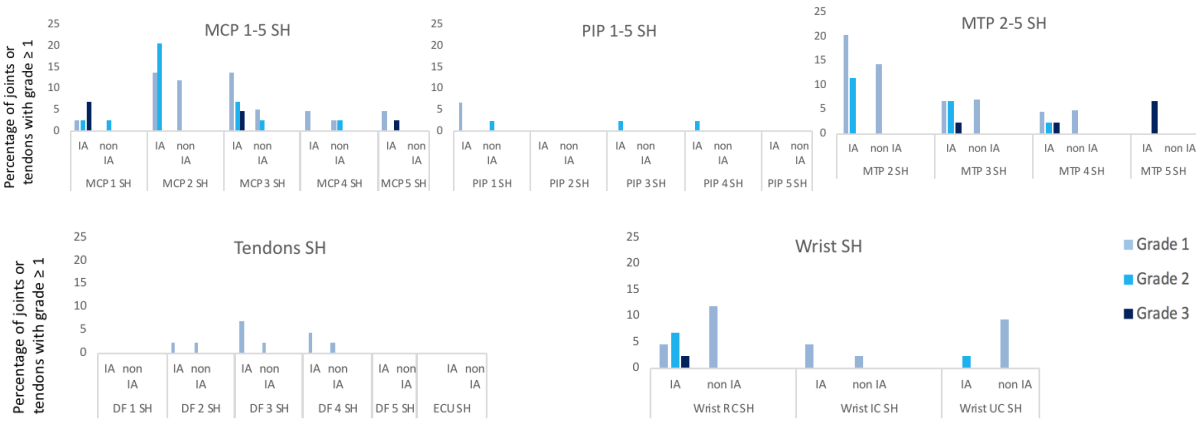

Figure 4-2 Bar charts of grade 1-3 synovial hypertrophy at baseline ultrasound in patients with and without inflammatory arthritis at 24-month visit

IA, inflammatory arthritis; MCP, metacarpophalangeal, joint PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon; RC, radio-carpal; IC, inter-carpal; UC, ulnar-carpal; SH, synovial hypertrophy; IA, inflammatory arthritis.

Figure 4-3 Bar charts of grade 1-3 Power Doppler at baseline ultrasound in patients with and without inflammatory arthritis at 24-month visit

MCP, metacarpophalangeal, joint PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon; RC, radio-carpal; IC, inter-carpal; UC, ulnar-carpal; PD, Power Doppler; IA, inflammatory arthritis.

The graphs in Figures 4-3 and 4-4 show the joints with most prevalence of grade ≥1 SH were in metacarpophalangeal joints (MCPJ) 2 and 3, metatarsophalangeal joint (MTPJ) 2 and the wrist joints. These joints also had the most PD grade ≥1 with the exception of the MTP joints

which had low levels of PD detected throughout. The only grade 3 SH and PD recorded were in the group of patients that went on to have IA by 24 months follow up.

4.5.5 Demographics of patients with Rheumatoid Arthritis or another inflammatory arthritis at 24 months

The group of patients with inflammatory arthritis at 24-month BEACON visit was split in to those patients with a diagnosis of RA, and those with a diagnosis of another inflammatory arthritis (see Table 4-10).

	RA at 24 months	Other IA at 24 months	p value
n	15	7	
Age, years, median (IQR)	45 (42, 56)	49 (31, 50)	0.672
BMI, median (IQR)	29.4 (24.6, 33.0)	30.3 (27.2, 34.0)	0.972
Female, n (%)	14 (93.3)	4 (57.1)	0.077
Ethnicity, n (%)	Caucasian 9 (60.0)	Caucasian 5 (71.4)	
Never smoked, n (%)	8 (53.3)	4 (57.1)	0.433
Symptom duration before diagnosis, wk,	70 (46, 161)	25 (16.0, 54.0)	0.129
< 1yr symptoms, n (%)	4 (26.7)	4 (57.1)	0.343
EMS, mins, median (IQR)	60 (5, 120)	120 (15, 120)	0.330
EMS ≥ 60 mins, n (%)	8 (53.3)	5 (71.4)	0.648
Symptoms in MCPs, n (%)	11 (73.3)	4 (57.1)	0.183
FH RA, n (%)	2 (13.3)	1 (14.3)	0.296
Tender MCPs, n (%)	9 (60.0)	2 (28.6)	0.361
Acute mode of onset, n (%)	3 (20.0)	2 (28.6)	0.632
Psoriasis history, n (%)	2 (13.3)	0 (0)	1.000
RF positive, n (%)	11 (73.3)	2 (28.6)	0.074
ACPA positive, n (%)	11 (73.3)	0 (0)	0.004
ESR, median (IQR)	23 (13, 32.8)	10 (2, 30)	0.135
CRP, median (IQR)	4 (2, 11)	3.0 (2.0, 8.0)	0.972
DAS 28 CRP, median (IQR)	3.61 (2.76, 4.56)	3.29 (1.81, 4.16)	0.459
DMARDs at 24 M, n (%)	10 (66.7)	5 (71.4)	0.100
Assessor global VAS, median (IQR)	18 (6, 21)	6 (5, 19)	0.247
Patient global VAS, median (IQR)	51 (39, 88)	48 (8, 74)	0.274
Patient pain VAS, median (IQR)	66 (29, 85)	47 (19, 72)	0.417
EMS patient VAS, median (IQR)	79 (42.5, 91.0)	58 (55, 90)	0.601
Fatigue severity VAS, median (IQR)	72 (48.0, 93.0)	59 (25, 80)	0.417
TJC 68, median (IQR)	6 (4, 19)	4 (2, 12)	0.288

Table 4-10 Baseline demographics and clinical data of patients with Rheumatoid arthritis or with another inflammatory arthritis at 24 months

RA, Rheumatoid Arthritis; IA, inflammatory arthritis; IQR, interquartile range; wk, weeks; mins, minutes; M, months; FH RA, first degree relative with RA; BMI, body mass index; CRP, C reactive protein; ESR, estimated sedimentation rate; DAS, disease activity score; EMS, early morning stiffness; TJC, tender joint count; VAS, visual analogue score.

ACPA positivity was significantly higher in the RA group (p=0.04) despite the sample size in both groups being small. There was a non-significant difference in Rheumatoid factor positivity between the groups (p=0.074), suggesting that ACPA is more specific in predicting the development of RA in patients with CSA.

4.5.6 Ultrasound data for patients with Rheumatoid Arthritis or another inflammatory arthritis at 24 months

The baseline visit ultrasound data for the CSA patients that went on to develop inflammatory arthritis were examined. These patients were separated in to those with a diagnosis of RA, and those with another form of inflammatory arthritis. Presence of grade 1-3 synovial hypertrophy and Power Doppler was compared between these two groups (Tables 4-11 and 4-12).

	RA at 24 months	Other IA at 24 months	RA vs other IA at 24M p value
Total number of joints	**30**	**14**	
MCP1 SH grade ≥1 n (%)	4 (13.3)	1 (7.1)	1.000
MCP2 SH grade ≥1 n (%)	9 (30.0)	6 (42.9)	0.501
MCP3 SH grade ≥1 n (%)	8 (26.7)	3 (21.4)	1.000
MCP4 SH grade ≥1 n (%)	1 (3.3)	1 (7.1)	0.540
MCP5 SH grade ≥1 n (%)	2 (6.7)	1 (7.1)	1.000
PIP1 SH grade ≥1 n (%)	2 (6.7)	1 (7.1)	1.000
PIP2 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
PIP3 SH grade ≥1 n (%)	1 (3.3)	0 (0.0)	1.000
PIP4 SH grade ≥1 n (%)	1 (3.3)	0 (0.0)	1.000
PIP5 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
MTP2 SH grade ≥1 n (%)	8 (26.7)	6 (42.9)	0.316
MTP3 SH grade ≥1 n (%)	6 (20.0)	1 (7.1)	0.401
MTP4 SH grade ≥1 n (%)	2 (6.7)	2 (14.3)	0.581
MTP5 SH grade ≥1 n (%)	3 (10.0)	0 (0.0)	0.540
Wrist RC SH grade ≥1 n (%)	5 (16.7)	1 (7.1)	0.647
Wrist IC SH grade ≥1 n (%)	1 (3.3)	1 (7.1)	0.540
Wrist UC SH grade ≥1 n (%)	0 (0.0)	1 (7.1)	0.318
Total number of tendons	**18**	**12**	
DF1 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
DF2 SH grade ≥1 n (%)	0 (0.0)	1 (7.1)	0.076
DF3 SH grade ≥1 n (%)	1 (3.3)	2 (14.3)	0.101
DF4 SH grade ≥1 n (%)	1 (3.3)	1 (7.1)	0.207
DF5 SH grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
ECU SH grade≥1 n (%)	0 (0.0)	0 (0.0)	n/a

Table 4-11 Baseline ultrasound of synovial hypertrophy in joints and tendons in clinically suspect arthralgia patients, with Rheumatoid Arthritis or other inflammatory arthritis at 24-months

IA, inflammatory arthritis; M, months; SH, synovial hypertrophy; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; RC, radio-carpal joint; IC, inter-carpal; joint UC, ulnar-carpal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon.

	RA at 24 months	Other IA at 24 months	RA at 24 months vs other IA at 24 months p value
Total number of joints	**30**	**14**	
MCP1 PD grade ≥1 n (%)	3 (10.0)	1 (7.1)	1.000
MCP2 PD grade ≥1 n (%)	8 (26.7)	3 (21.4)	1.000
MCP3 PD grade ≥1 n (%)	5 (16.7)	3 (21.4)	0.695
MCP4 PD grade ≥1 n (%)	1 (3.3)	1 (7.1)	0.540
MCP5 PD grade ≥1 n (%)	1 (3.3)	1 (7.1)	0.540
PIP1 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
PIP2 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
PIP3 PD grade ≥1 n (%)	1 (3.3)	0 (0.0)	1.000
PIP4 PD grade ≥1 n (%)	1 (3.3)	0 (0.0)	1.000
PIP5 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
MTP2 PD grade ≥1 n (%)	0 (0.0)	1 (7.1)	0.318
MTP3 PD grade ≥1 n (%)	1 (3.3)	0 (0.0)	1.000
MTP4 PD grade ≥1 n (%)	1 (3.3)	0 (0.0)	1.000
MTP5 PD grade ≥1 n (%)	3 (10.0)	0 (0.0)	0.540
Wrist RC PD grade ≥1 n (%)	5 (16.7)	1 (7.1)	0.647
Wrist IC PD grade ≥1 n (%)	0 (0.0)	1 (7.1)	0.318
Wrist UC PD grade ≥1 n (%)	0 (0.0)	1 (7.1)	0.318
Total number of tendons	**18**	**12**	
DF1 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
DF2 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
DF3 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
DF4 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
DF5 PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a
ECU PD grade ≥1 n (%)	0 (0.0)	0 (0.0)	n/a

Table 4-12 Baseline ultrasound of Power Doppler joints and tendons in clinically suspect arthralgia patients, with Rheumatoid Arthritis or other inflammatory arthritis at 24-months

IA, inflammatory arthritis; PD, Power Doppler; MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; RC, radio-carpal joint; IC, inter-carpal; joint UC, ulnar-carpal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon.

The sample sizes for the RA and other IA groups were small, which may be why there were no significant differences in prevalence of grade ≥1 SH or PD in joints and tendons between the two groups. The severity of the SH and PD appears to be more of grade 1 and 2 (Figures 4-5 and 4-6) with no obvious difference in prevalence in grade 3 between the RA and other IA groups. There were fewer grade ≥1 SH and PD finding in the proximal interphalangeal joints (PIPJs) compared to the other joints.

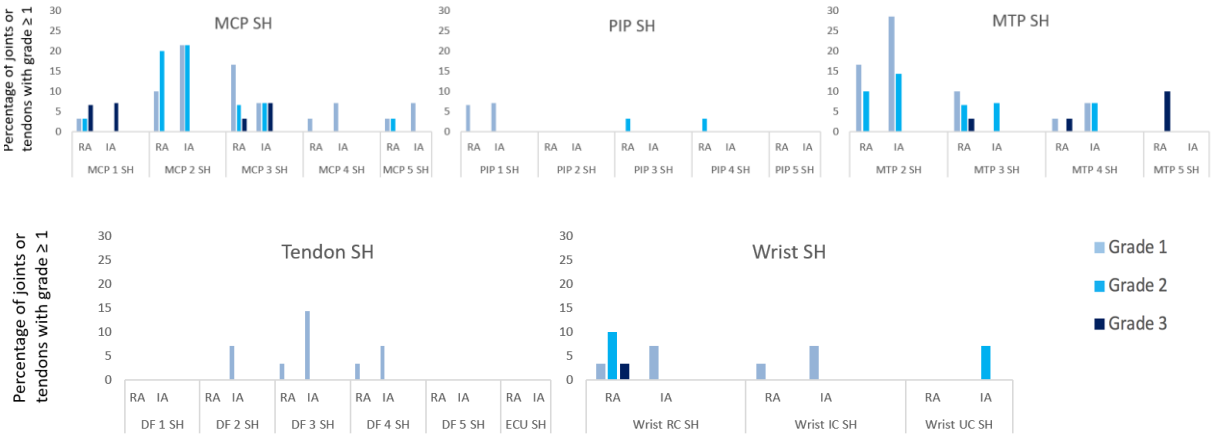

Figure 4-4 Bar charts of grade 1-3 synovial hypertrophy at baseline ultrasound in patients with Rheumatoid Arthritis or another inflammatory arthritis at 24-month visit

RA, Rheumatoid Arthritis; IA, inflammatory arthritis; MCP, metacarpophalangeal, joint PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon; RC, radio-carpal; IC, inter-carpal; UC, ulnar-carpal; SH, synovial hypertrophy; IA, inflammatory arthritis.

Figure 4-5 Bar charts of grade 1-3 Power Doppler at baseline ultrasound in patients with Rheumatoid arthritis or another inflammatory arthritis at 24-month visit

RA, Rheumatoid Arthritis; IA, inflammatory arthritis; MCP, metacarpophalangeal, joint PIP, proximal interphalangeal joint; MTP, metatarsophalangeal joint; DF, digit flexor tendon; ECU, extensor carpi ulnaris tendon; RC, radio-carpal; IC, inter-carpal; UC, ulnar-carpal; SH, synovial hypertrophy; IA, inflammatory arthritis.

4.6 Discussion

The ability to predict which patients with joint pain but without clinical synovitis go on to develop RA or another inflammatory arthritis is important as it will help guide clinical decision making and reduce patient morbidity. In this study, Rheumatoid factor positivity was

significantly associated with CSA patients progressing to an inflammatory arthritis, and Anti-CCP positivity was significantly associated with development of Rheumatoid arthritis within two years after diagnosis of CSA. This is already known from previous studies.[155 72]

The ultrasound data on CSA patients at time of diagnosis revealed there was significantly more grade ≥ 1 SH in MCPJ 2 and 3 in those patients that progressed to an inflammatory arthritis by 24 months follow up ($p<0.05$). Also, there were only grade 3 SH or PD in the group that went on to have IA. This suggests that presence of synovial hypertrophy on baseline ultrasound in MCPJ 2 and 3 may predict those CSA patients that will go on to develop IA within the next 2 years. Prevalence of PD grade ≥ 1 was not significantly higher in the group that went on to have IA. Another study of 163 patients with arthralgia also found presence of abnormal SH on MSUS in MCP 2-3, PIPJ 2-3 and/or wrists was significantly associated with development of inflammatory arthritis, but the same association was not seen with presence of PD.[146] Other studies have suggested that presence of PD on US may predict development of RA.[231-233]

This study unfortunately had a small sample size of patients with clinically suspect arthralgia at baseline assessment, who also had the required follow up data 24 months later. The exclusion criteria needed to be rigid to ensure all relevant follow up clinical data and baseline ultrasound assessments were available and reliable. The COVID-19 pandemic also impacted upon the sample number, as several CSA patients had a 24-month BEACON visit postponed due to lockdown in 2020. Some 24 month CSA data has also been lost by patients not attending follow up study visits; many of these lost to follow up patients may have had resolution of their joint problems so not including this follow up data may skew results.

Further limitations in this study include the different ultrasound machines used at Queen Elizabeth and City Hospitals in Birmingham. However, they had been centrally calibrated before being moved to different sites, were from the same manufacturer with similar operating systems, and used the same probes. Also there were several sonographers who had scanned patients over several years. The CSA patients scanned by one sonographer were excluded as images were not available to be able to perform reliability studies. The Kappa co-efficient for reliability studies was weak and moderate for the two sonographers. However, this is comparable to other similar studies[232 234] and at the lower end of the range inter-observer reliability scores seen with an OMERACT consensus study.[235] In future, data from this study will be more reliable as more scans will be from a fewer number of sonographers.

It is possible that the initiation and continued treatment with DMARDs in the CSA group (of which there were 5/21 at 24-month diagnosis) may have prevented the manifestation of persistent inflammatory arthritis. Particularly because three of these patients had at least one joint with evidence of synovitis on baseline ultrasound. This may have skewed the results, therefore it may have been helpful to run additional analysis to include the five patients in the "non-IA at 24 months" group who were on DMARDs, with the IA group, and compare against the remaining 16 non-IA patients.

The presence of tenosynovitis on ultrasound in CSA patients has been suggested in other studies as a helpful predictive tool in determining the development of persistent RA from an unselected inception cohort of new onset inflammatory arthritis.[150] Unfortunately there were not many data on tendons available in this study because tendons only became part of the ultrasound scanning protocol more recently, meaning it was missing for CSA patients recruited earlier on.

There is a gap in the literature on tendon data and prediction of patients with arthralgia going on to develop inflammatory arthritis.[236]

Some of the information with regards to the EULAR consensus criteria for CSA were not collected prior to its publication such as: ability to form a fist, symptoms being worse in the mornings, and symptoms located in the MCP joints. These variables are now formally collected via BEACON assessment forms to allow evaluation in future research projects.

Comparison of the baseline characteristics of those CSA patients that went on to develop IA within 2 years and those that did not, showed that the non-IA group had significantly more CSA patients with less than one year duration of arthralgia symptoms before initial diagnosis, which is contrary to what is suggested by the EULAR consensus criteria. There were more patients in the non-IA group with tender MCPJs (taken as an implication these patients would have had a positive MCP squeeze test) at baseline assessment (p=0.055), which again contradicts the EULAR consensus criteria for CSA. The CSA consensus criteria may mean that patients with musculoskeletal complaints were more likely to be diagnosed with CSA if they had a relatively short duration of symptoms and if they had a positive MCP squeeze test, but these two clinical features may not actually be predictive of development of IA. In a study of 315 CSA patients, positive MCP squeeze test was not predictive of development of IA.[237] There is little evidence in the literature for duration of CSA symptoms less than 12 months being associated with progression to RA, with some studies excluding CSA patients with a longer duration of symptoms.[238] A study of 465 patients with unselected hand arthralgia found duration of symptoms less than one year and MCP squeeze test both significantly associated with development of RA but these patients did not all have CSA at baseline.[231]

This study has revealed some interesting information with some significant results despite having small number of CSA patients. Similar to other studies RF, and ACPA were associated with development of RA, and SH grade ≥ 1 in MCP 2 and 3 was associated with progression to IA. Contrary to other studies presence of PD grade ≥ 1 was not associated with development of RA, but one study has suggested that MSUS is not helpful at all as a predictive tool in CSA.[234] This study aimed to test the validity of the seven EULAR consensus criteria for CSA and found a higher prevalence of CSA patients in the group that did not progress in to IA had a positive MCP squeeze test, and although this was not significant it was similar to another larger study.[237] Also, more CSA patients who did not progress to IA had a duration of symptoms less than 1 year, which is again contrary to what is expected and needs further investigation. Within the next one to two years there should be more 24-month BEACON visit data available for these patients which should expand the study size allowing further analysis of the EULAR CSA consensus criteria, and also further evaluation of the clinical and ultrasound features of CSA patients that may predict those who go on to progress to RA. In future studies, observing composite ultrasound joint count data rather than just individual joint data may improve the study power and ability to draw significant conclusions. CSA ultrasound data may also be compared against the ultrasound data for joints and tendons from the healthy subjects in this thesis, to determine if patients with CSA have different ultrasound findings than would be expected in the normal healthy population.

5 GENERAL DISCUSSION

The main body of work in this thesis was the OMERACT minimal disease project where collaboration between 23 international centres has resulted in a study of >900 healthy subjects (HS) to study ultrasound findings in joints across the age range. The aim was to define normal age-related findings on ultrasound in healthy subjects at the ages when RA typically presents, thus providing an age-based reference range to interpret ultrasound results for patients presenting with symptoms that may represent undiagnosed early inflammatory arthritis.

The ultrasound data on digit flexor (DF) and extensor carpi ulnaris (ECU) tendons in HS across the age range has been published in the Annals of the Rheumatic Diseases and will hopefully provide control data for future studies on tendons in Rheumatology ultrasound. Inflammation in tendons may be an important indicator of progression of inflammatory arthritis. The abstract of this data, presented orally at the American College of Rheumatology conference in November 2018, has already been cited by one paper indicating that the published full tendon data will be referenced by many future Rheumatology ultrasound studies.

The eventual publication of the HS joint ultrasound data should similarly provide important healthy control data for future studies. Unfortunately, my thesis does not contain the final joint data because a centralised regrading exercise of all images will first take place, and is beyond the scope of my thesis. In hindsight, before data collection began there should have been more extensive reliability studies. However, it was unexpected that there would be such inconsistencies in joint grading as all the collaborating centres were all very experienced OMERACT contributors.

The production of MSUS grading atlases for MTPJs and wrist joints was an unexpected side project, but it should be a useful educational resource for future OMERACT projects, future ultrasound research and also clinicians scanning these joints in clinic. It is important this study has highlighted consistencies in grading these joints, and now with further education and reference resources Rheumatology sonographers should be grading these joints more consistently.

A minor drawback of the protocol of the minimal disease study was that it did not initially list all the final exclusion criteria for HS such as pregnancy and history of autoimmune conditions. It was only through a data cleaning exercise that it became apparent the exclusion criteria were not broad enough. It would also have also been helpful to record dominant side in all centres. The recording of occupations and physical hobbies could have been more specific to facilitate analysis of results.

A limitation of the minimal disease study was that the HS were very healthy and had no joint pain. The CSA project in Chapter 4 aimed to examine the clinical and ultrasound features of patients with inflammatory joint pain and identify which patient went to go on to have RA or IA. Unfortunately, the CSA data was impacted in part by COVID-19 and did not include enough patients with 24 month follow up data to draw significant conclusions. However, in the near future the department should have more CSA patients with 24 month follow up data. There will also be less sonographers performing the scans to reduce reliability issues.

The minimal disease study excluded patients with a diagnosis of osteoarthritis (OA) according to ACR criteria. This may not have fully exclude all Hs with OA because it requires presence of hand pain or stiffness in additional to clinical examination findings of OA, therefore some

HS with mild asymptomatic hand OA may have been recruited. The exclusion of OA makes the real world applicability of this data more difficult because it is very common in the general population, particularly in the age range that RA typically presents. However, another OMERACT ultrasound working group is examining ultrasound findings of OA.

This thesis presents data on what is currently the largest cohort of HS throughout the age range with ultrasound findings. With the CSA data we have given an example of its applicability in future research.

Word count 27618

6 Appendices

Appendix 1 Minimal Disease Study Protocol

ULTRASOUND WORKING GROUP
MINIMAL DISEASE SUB-TASK FORCE
STUDY PROTOCOL

Lead: Dr Andrew Filer
OMERACT US Fellow: Dr Ilfita Sahbudin
Mentor: Professor Maria Antonietta D'Agostino

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1 Background

Musculoskeletal ultrasound (MSUS) is more sensitive and specific compared to clinical examination in the detection of joint synovitis in inflammatory arthritis patients [1] and is increasingly utilised as a point-of-care tool in Rheumatology. MSUS is increasingly used to diagnose early arthritis, monitor treatment response [2] and detect subclinical disease in patients who are in apparent clinical remission [3].

However, the difference between ultrasound changes observed in normal joints (i.e. physiological changes) and those seen in early arthritis joints (i.e. early pathological changes) is poorly defined. In addition, there has been significant improvement in ultrasound technology over the last ten years which results in higher image resolution. As a result, MSUS is now able to detect minimal changes even in healthy individuals with no joint symptoms [4].

Defining the concept of ultrasound-detected 'minimal disease' is crucial in order to i) define the time of onset in early disease, ii) define minimal response to treatment, and iii) identify remission in patients with inflammatory arthritis.

2 Aim

The aim of this study is to define the threshold of at which ultrasound findings should be considered pathological at the joint level in patients with early arthritis.

2.1 Objective

To systematically document ultrasound findings (synovial hypertrophy, synovial effusion and Power Doppler) in the joints of healthy asymptomatic individuals who are above the age of 18.

3 Participant Criteria

3.1 Inclusion criteria

- Age ≥ 18.

3.2 Exclusion criteria

- Previous/current inflammatory joint disease (including crystal arthropathy).
- Visual analogue score (VAS) for joint pain > 10/100.
- Any history of joint trauma in the last month.
- Fulfilling hand osteoarthritis ACR criteria (Appendix 1).
- Any clinical joint inflammation as identified by a physician.
- Previous or current inflammatory bowel disease.
- History of culture-proven enteric and/or genitourinary infection in the last month.
- Current or previous corticosteroids use in the last 4 weeks.
- Current non-steroidal anti-inflammatory use.

4 Ultrasound Assessments

4.1 Joint and tendon sub-set

1. There are two levels of US data acquisition for this study (Table 1).
   a. Level 1: Mandatory ultrasound lesion
   b. Level 2: Optional ultrasound lesion

Table 1: List of mandatory and optional ultrasound lesion

Level	1 (mandatory)	2 (optional)
Ultrasound lesion	i. Joint synovial hypertrophy ii. Joint synovial effusion iii. Joint synovial Power Doppler iv. Tenosynovial hypertrophy v. Tenosynovial effusion vi. Tenosynovial Power Doppler	i. Osteophyte ii. Erosion (only for MCP 2 & 5, MTP 5)

2. The joint and tendon sites to be scanned are listed in Table 2 below.

Table 2: Joint and tendon sub-set

Structure	Site
Joint	i. MCPs 1-5 ii. PIPs 1-5 iii. Wrist Inter-carpal, Radio-carpal & Ulnar-carpal iv. MTP 1-5
Tendon	i. Finger flexor tendon 1-5 ii. Extensor carpi ulnaris tendon

3. The following grading of grey-scale and power Doppler will be documented for each joint:

Table 3: Grading system for joint sites

Grey-scale	Synovial hypertrophy	Semi-quantitative 0-3
	Synovial effusion	Semi-quantitative 0-3
Power Doppler (PD)	PD severity	Semi-quantitative 0-3
Degenerative	Presence of osteophyte	Semi-quantitative 0-3
Erosion	Presence of erosion (only for MCP2, 5 and MTP5)	Yes/No

4. The following grading of grey-scale and power Doppler will be documented for each tendon:

Table 4: Grading system for tendon sites

Grey-scale	Tenosynovial hypertrophy	Semi-quantitative 0-3
	Tenosynovial effusion	Yes/No
Power Doppler (PD)	PD grading	Semi-quantitative 0-3

4.2 Grading definitions

1. The **joint** ultrasound elementary lesions to be recorded **are synovial hypertrophy, effusion** and **Power Doppler Enhancement**. Each US elementary lesion should be graded according to the EULAR-OMERACT consensus definition [5, 6] as detailed in Table 5-7 below.

Table 5: Grading definition for joint synovial hypertrophy US elementary lesion [5, 6]

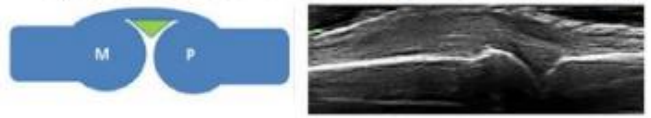
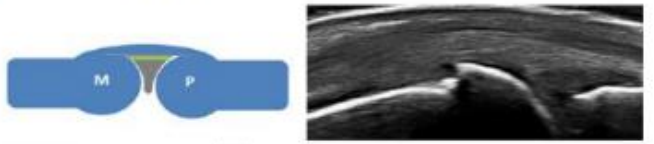
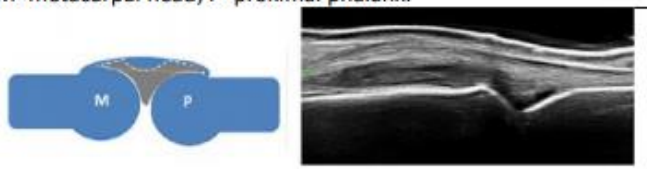
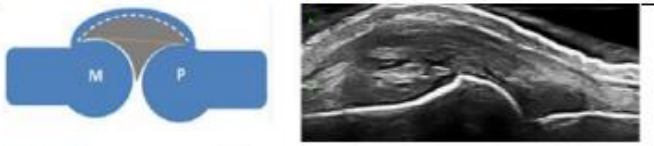
Joint synovial hypertrophy	Definition of grading	Representative schematic diagram and US images
Abnormal hypoechoic intra-articular tissue or **higher echoic** (relative to subdermal fat) **that is not or poorly displaceable,** and which may exhibit Doppler signal.	**Grade 0** (none) No synovial hypertrophy independently of the presence of effusion.	 Loose intra-articular connective tissue; M=metacarpal head; P=proximal phalanx.
	Grade 1 (minimal) **Minimal hypoechoic** synovial hypertrophy **up to the level of the horizontal line** connecting bone surfaces between the metacarpal head and the proximal phalanx.	 Joint line Hypertrophy Connective tissue M=metacarpal head; P=proximal phalanx.
	Grade 2 (moderate) **Moderate hypoechoic** synovial hypertrophy **extending beyond joint line but with the upper surface concave** (curved downwards) or **hypertrophy extending beyond the joint line but with the upper surface flat.**	 Joint line; Hypertrophy; M=metacarpal head; P=proximal phalanx.
	Grade 3 (severe) **Severe hypoechoic** synovial hypertrophy with or without effusion **extending beyond the joint line but with the upper surface convex (curved upwards).**	 Joint line Hypertrophy; M=metacarpal head; P=proximal phalanx.

Table 6: Grading definition for Power Doppler US elementary lesion [5, 6]

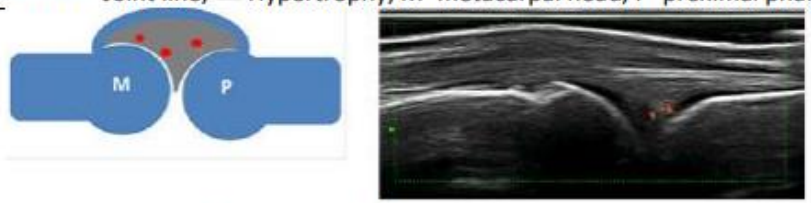
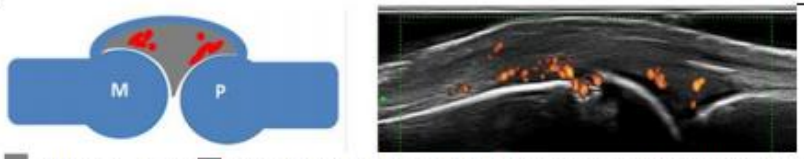
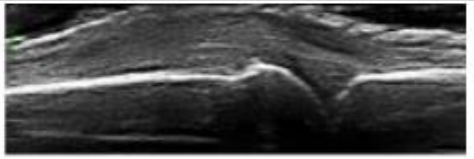
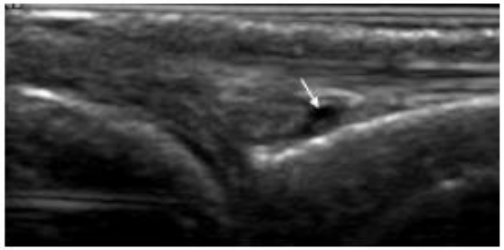
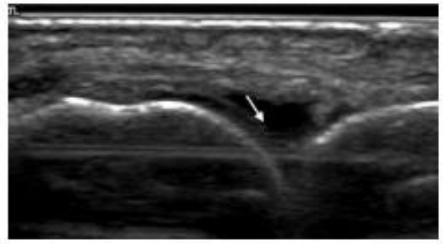
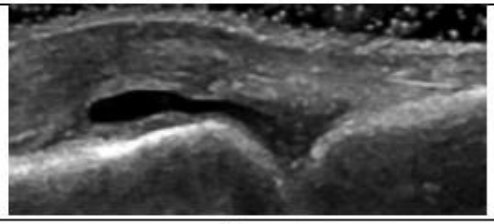
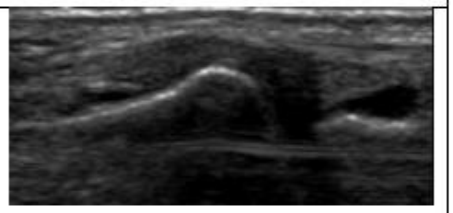
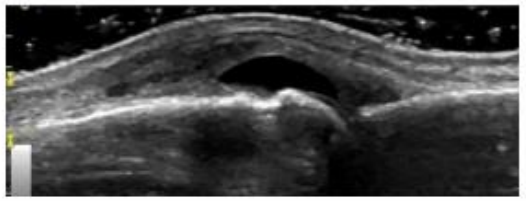
Joint Power Doppler	Definition of grading	Representative schematic diagram and US images
Abnormal vascularization detected within the hypoechoic synovial hyperplasia.	**Grade 0** (none) No Doppler signal	 Joint line; Hypertrophy; M=metacarpal head; P=proximal phalanx.
	Grade 1 (minimal) Up to **three single Doppler spots** OR up to **one confluent spot and two single spots** OR up to **two confluent spots.**	 Hypertrophy; Intra-synovial Doppler; M=metacarpal head; P=proximal phalanx.
	Grade 2 (moderate) Greater than Grade 1 but **≤50% Doppler signals in the total greyscale background**.	 Hypertrophy; Intra-synovial Doppler; M=metacarpal head; P=proximal phalanx.
	Grade 3 (severe) Greater than Grade 2 **(>50% of the total greyscale background**).	 Hypertrophy; Intra-synovial Doppler; M=metacarpal head; P=proximal phalanx.

Table 7: Grading definition for joint effusion US elementary lesion [2]

Joint effusion	Definition of grading	Representative US images
Abnormal anechoic or hypoechoic (relative to subdermal fat) intraarticular material that is **easily displaceable**, but does not exhibit Doppler signal.	**Grade 0** No effusion	
	Grade 1 **Minimal** amount of joint effusion	 
	Grade 2 **Moderate** amount of joint effusion (little distension of the joint capsule)	 
	Grade 3 **Extensive** amount of joint effusion (with high distension of the joint capsule)	

2. The **tendon** ultrasound elementary lesions to be recorded **are synovial hypertrophy, effusion** and **Power Doppler Enhancement**. The grading system for each US elementary lesion is according to the EULAR-OMERACT consensus definition [7] and detailed in Table 8 below.

Table 8: Grading definition for tenosynovial hypertrophy US elementary lesion [7]

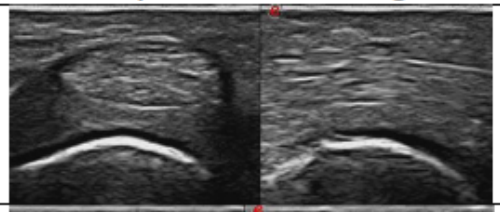
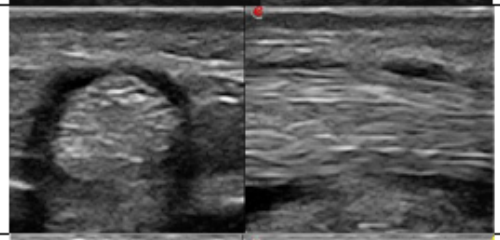
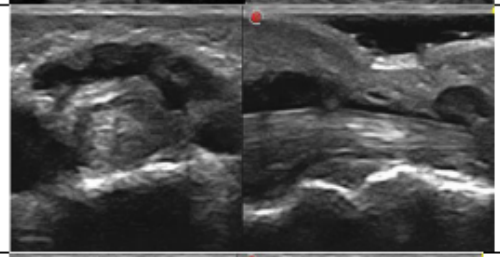
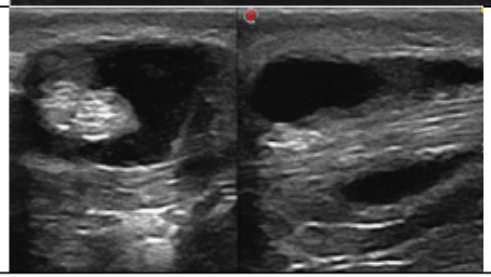
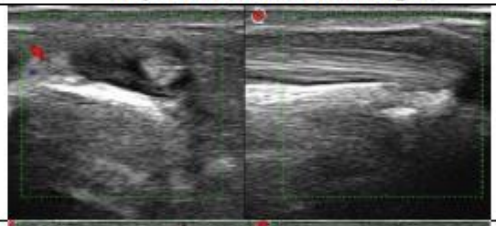
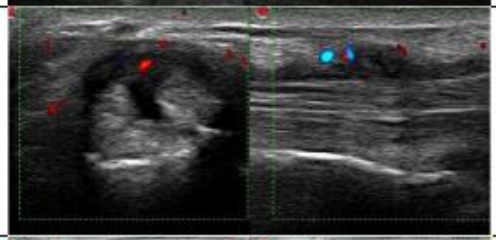
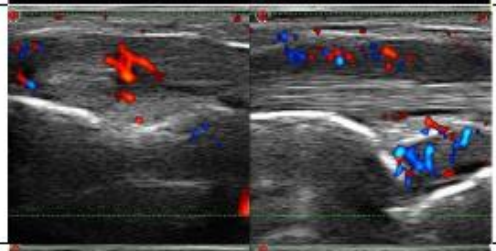
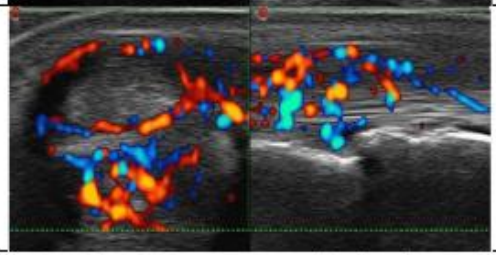
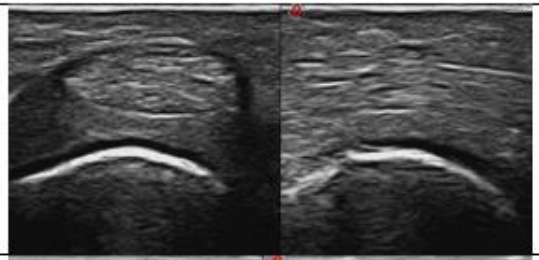
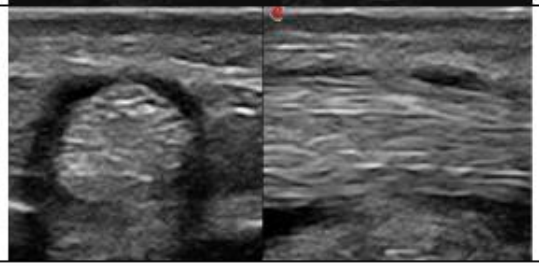
Tenosynovial hypertrophy [7]	Definition of grading	Representative US images
Abnormal hypoechoic (relative to tendon fibres) tissue within the tenosynovial sheath that **is not displaceable and poorly compressible** and seen in two perpendicular planes.	**Grade 0** No abnormal hypoechoic within the tenosyovial sheath	
	Grade 1 Minimal abnormal hypoechoic within the tenosyovial sheath	
	Grade 2 Moderate abnormal hypoechoic within the tenosyovial sheath	
	Grade 3 Severe abnormal hypoechoic within the tenosyovial sheath	

Table 9: Grading definition for tenosynovial Doppler US elementary lesion [7]

Tenosynovial Doppler	Definition of grading	Representative US images
Presence of peritendinous Doppler signal within the synovial sheath, seen in two perpendicular planes, excluding normal feeding vessels (i.e. vessels at the mesotenon or vinculae or vessels entering the synovial sheath from surrounding tissues) **only if the tendon shows peritendinous synovial sheath widening on B-mode**	**Grade 0** No signal	
	Grade 1* **Peritendinous focal signal** within the widened synovial sheath (i.e. signals in **only one area** of the widened sheath), seen in two perpendicular planes, excluding normal feeding vessels;	
	Grade 2* **Peritendinous multifocal signal** within the widened synovial sheath (i.e. signals in **more than one area** of the widened sheath), seen in two perpendicular planes, excluding normal feeding vessels;	
	Grade 3 **Peritendinous diffuse signal** within the widened synovial sheath (i.e. signals **filling most of the widened sheath**), seen in two perpendicular planes, excluding normal feeding vessels.	

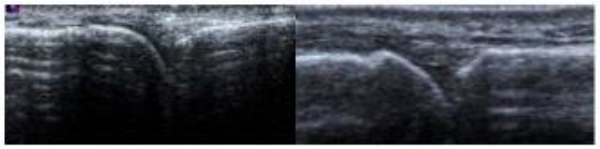
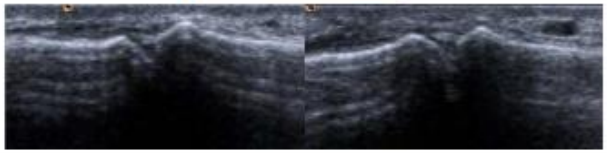
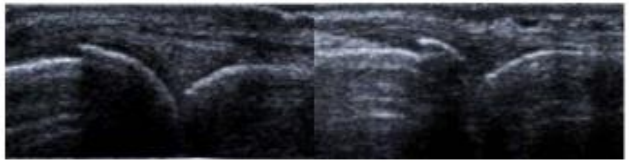
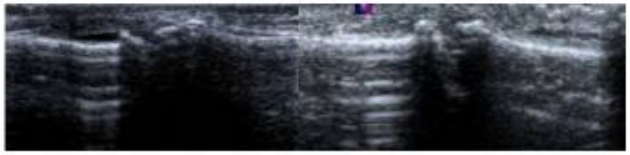
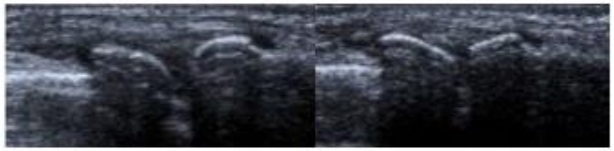
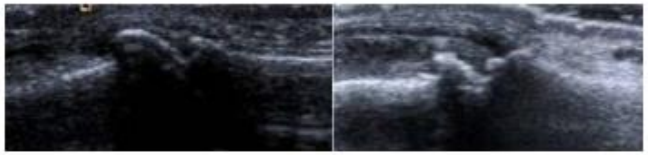
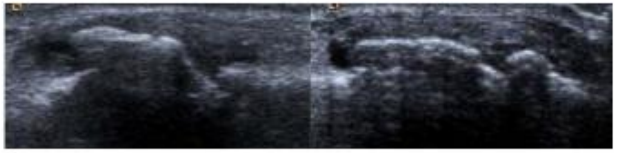
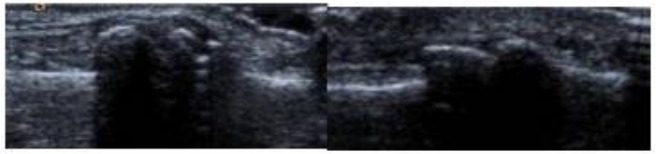
*If **in addition to an abnormal peritendinous** (i.e. intra-sheath) signal there was an **abnormal intratendinous signal** seen in two perpendicular planes (i.e. excluding intra-tendinous small isolated signals that can correspond to normal feeding vessels detectable by US), **then grades 1 and 2 would be increased by one point.**

Table 10: Grading definition for tenosynovial effusion US elementary lesion [7]

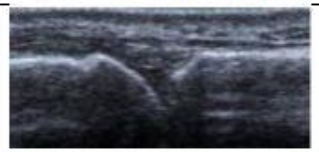
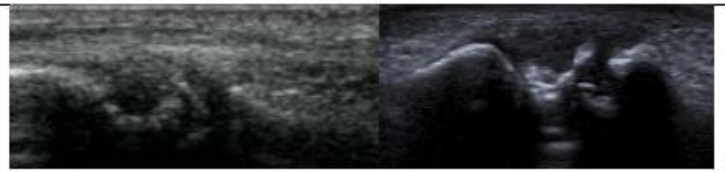
Tenosynovial effusion	Definition of grading	Representative US images
Abnormal anechoic or hypoechoic (relative to tendon fibres) material within the synovial sheath, either localised (eg, in the synovial sheath cul-de-sacs) or surrounding the tendon **that is displaceable** and seen in two perpendicular planes	**Absent** No abnormal displaceable hypoechoic region within the tenosyovial sheath	
	Present Presence of at least minimal abnormal hypoechoic within the tenosyovial sheath	

3. The recording of **osteophytes is optional** for this study. The definition and grading of osteophytes are detailed as below.

Table 11: Definition and grading system of osteophytes [8, 9].

Osteophytes	Definition of grading	Representative US images MCP joint	Representative US images of PIP joint
A step-up bony prominence at the end of the normal bone contour, or at the margin of the joint seen in two perpendicular planes, with or without acoustic shadow.	**Grade 0** No osteophytes, i.e. a smooth cortical surface.		
	Grade 1 Small and distinct cortical protrusion(s) of the bony surface.		
	Grade 2 Larger protrusion(s) which may have broad base(s).		
	Grade 3 Very large protrusion(s) which may have very broad base(s).		

3. The recording of **erosions** is optional for this study and only limited to MCP2, 5 and MTP 5. The definition and grading of the osteophytes are detailed as below.

Erosions [10]	Definition of grading	Representative US images
A cortical "break" or defect with an irregular floor seen in longitudinal and transverse planes.	**Absent** No erosion	
	Present Erosion present	

4.3 US images record and data input

1. All images should be recorded according to the EULAR Working Group for Musculoskeletal Ultrasound 2017 recommendation [11].
2. All structures should be scanned using both longitudinal and transverse approaches.
3. However, only longitudinal views are recorded for joint scanning, and longitudinal and transverse views are recorded for tendon scanning (see Table 13).

Table13: Views to be recorded for joint and tendon core set

Region	Joint and tendon core set	Views to be recorded
Hand	MCP 1-5	Longitudinal
	PIP 1-5	
	Flexor tendon 1-5	Longitudinal & transverse
Wrist	Inter-carpal, Radio-carpal, Ulnar-carpal	Longitudinal
	Extensor Carpi Ulnaris tendon	Longitudinal & transverse
Foot	MTP 1-5	Longitudinal

4. All images and US scores from the first participant should be compiled onto a power point presentation and emailed to Dr Sahbudin (as soon as feasible.
5. At the end of the study, all images must be anonymised and recruiting centres will contact Dr Ilfita Sahbudin to liaise the transfer of the US images of all healthy participants along with the US scores. The US scores should be compiled onto the excel spreadsheet that has been provided.
6. The following details should be recorded on the US images for each participant
    a. Date of visit
    b. Participant research ID (i.e. anonymised)
    c. Joint or tendon site using the abbreviations as shown in the table 14:

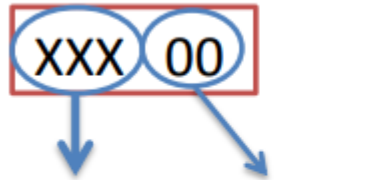
Table 14: Abbreviation for recorded US images

Right or left	Joint/tendon site	Number of position
R, L	MCP	1-5
	PIP	1-5
	MTP	1-5
	Wrist	IC/RC/ UC
	DF	1-5
	ECU	

Example:

i. L DF 1
ii. R MCP 5
iii. R ECU
iv. L wrist UC
v. L MTP 5

7. Each centre should assign a unique research ID for each healthy subject participant in the following format:



E.g. The 30 healthy participants recruited at University Hospital Birmingham, UK, would have the following consecutive research IDs:

UHB 01 – UHB 30.

4.4 Joint positioning

The hand should be positioned flat on the table in a relaxed position as shown in Figure 1 below. Flexor tendon scanning should be done at the level of the MCP joint. For foot scanning, the participant should be placed on a couch with the knees flexed and foot flat on the couch (Figure 2).

Figure 1: Hand position during joint scanning

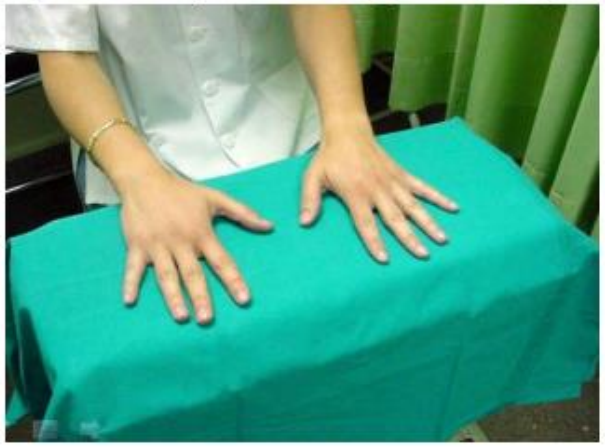
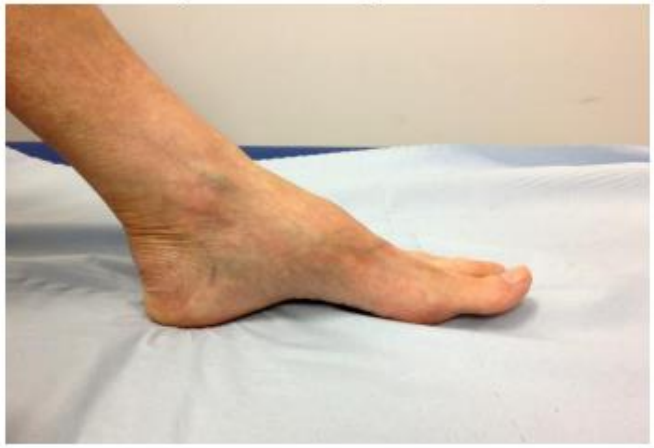


Figure 2: Foot position during joint scanning



5 Clinical Assessment

1. Clinical details from section 5.1 and 5.2 will be recorded for all participating healthy individuals on the clinical proforma (provided).
2. At the end of the study, all clinical proforma should be scanned and transferred to Dr Sahbudin along with the documents listed in appendix 2.

5.1 History

a. Age
b. Sex
c. Personal history of skin psoriasis
d. Family history of

i. osteoarthritis,
ii. skin psoriasis,
iii. inflammatory arthritis,
iv. connective tissue disease,
v. Inflammatory bowel disease.

e. Previous trauma/joint replacement (specify joint)
f. Hobbies
g. Occupation; if retired previous occupation
h. Current medication
i. Co-morbidities
j. Smoking status

5.2 Examination

a. Visual analogue scale for overall joint pain
b. Swollen and tender joint assessment: MCP 1-5, PIP 1-5, wrist, MTP 1- 5
c. Record presence of clinical MTP1 degenerative disease
d. Height and weight

6 Recruitment and Sample Size

This is a cross-sectional study with the main recruitment centres at University Hospital Birmingham, UK and Ambroise Pare Hospital, Boulogne-Billancourt, France. Additional OMERACT recruitment centres will be involved by invitation. The target recruitment is 200 healthy individuals.

7 Appendices

Appendix 1

The ACR criteria for the classification of osteoarthritis of the hand*

Hand pain, aching, or stiffness, and

3 or 4 of the following features:

- Hard tissue enlargement of 2 or more of 10 selected joints
- Fewer than 3 swollen MCP joints
- Hard tissue enlargement of 2 or more DIP joints
- Deformity of 1 or more 10 selected joints

*The 10 selected joints are the second and third DIP, the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands.

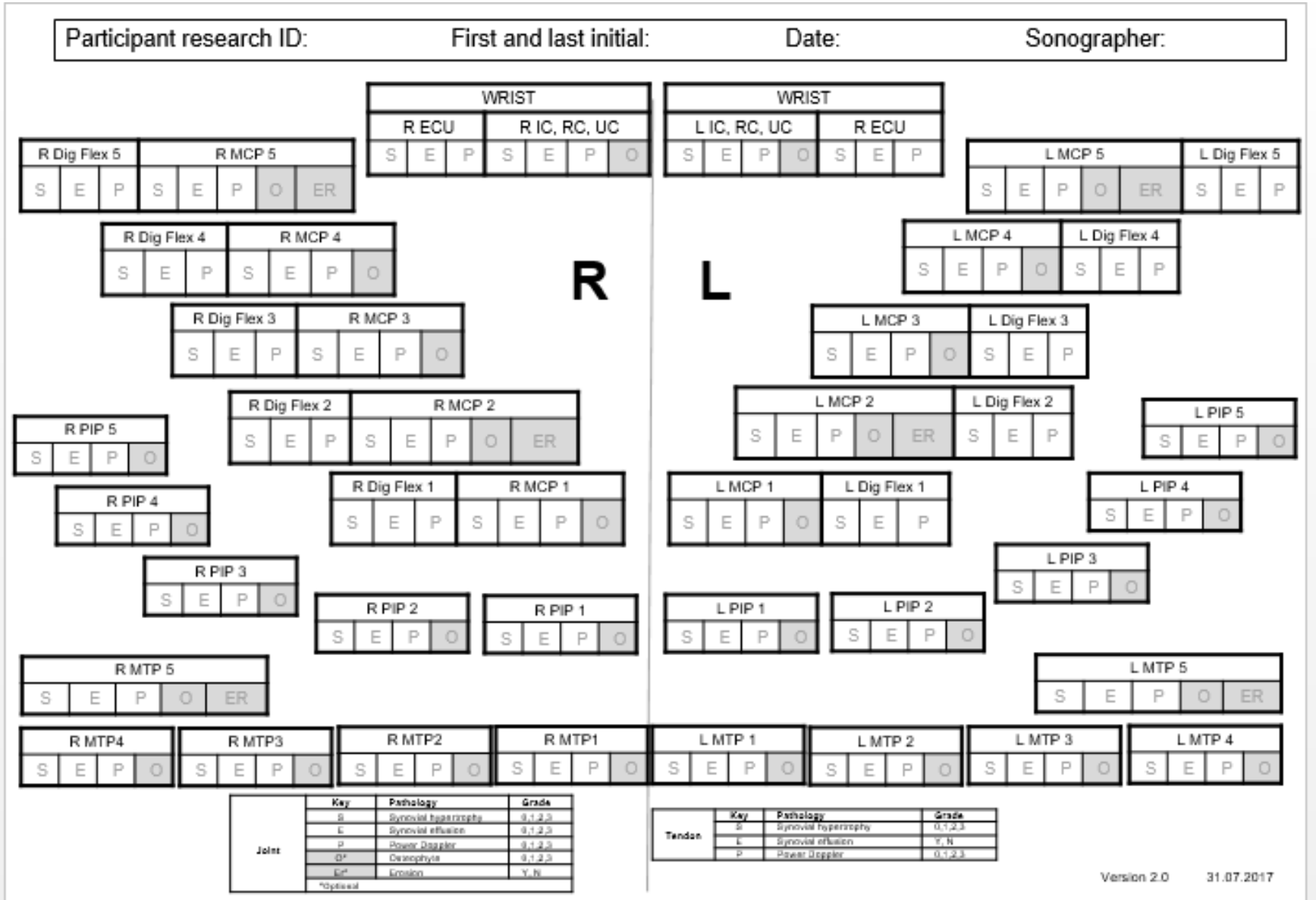
Appendix 2

Upon completion of recruitment and data collection, these documents should be transferred to Dr Sahbudin [redacted]

1. Anonymised US images for all healthy participants.
2. Compiled US gradings for all healthy participants in excel spreadsheet.
3. Scanned copies of individual clinical proforma.

8 References

1. Wakefield RJ, Green MJ, Marzo-Ortega H, Conaghan PG, Gibbon WW, McGonagle D, Proudman S, Emery P. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. Ann Rheum Dis. 2004 Apr; 63(4):382-385.
2. D'Agostino MA, Boers M, Wakefield RJ, Berner Hammer H, Vittecoq O, Filippou G, Balint P, Moller I, Iagnocco A, Naredo E, Ostergaard M, Gaillez C, Le Bars M. Exploring a new ultrasound score as a clinical predictive tool in patients with rheumatoid arthritis starting abatacept: results from the APPRAISE study. RMD Open. 2016; 2(1):e000237.
3. Dejaco C, Duftner C, Wipfler-Freissmuth E, Weiss H, Graninger WB, Schirmer M. Ultrasound-defined remission and active disease in rheumatoid arthritis: association with clinical and serologic parameters. Semin Arthritis Rheum. 2012 Jun; 41(6):761-767.
4. Padovano I, Costantino F, Breban M, D'Agostino MA. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. Ann Rheum Dis. 2015 Nov 27.
5. Terslev L, Naredo E, Aegerter P, Wakefield RJ, Backhaus M, Balint P, Bruyn GA, Iagnocco A, Jousse-Joulin S, Schmidt W, Szkudlarek M, Conaghan P, Filippucci E, D'Agostino M A. Scoring ultrasound synovitis in rheumatoif arthritis: a EULAR-OMERACT ultrasound taskforce-Part 2: Reliability and application to multiple joints of a standardised consensus-based scoring system. Rheumatic & Musculoskeletal Diseases Open 2017; 3:e000427.
6. D'Agostino M A, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, Filippucci E, Grassi W, Iagnocco A, Jousse-Joulin S, Kane D, Naredo E, Schmidt W, Szkudlarek M, Conaghan P, Wakefield RJ. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. Rheumatic & Musculoskeletal Diseases Open. 2017; 3:e000428.
7. Naredo E, D'Agostino MA, Wakefield RJ, Moller I, Balint PV, Filippucci E, Iagnocco A, Karim Z, Terslev L, Bong DA, Garrido J, Martinez-Hernandez D, Bruyn GA, Force* OUT. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis. 2013 Aug; 72(8):1328-1334.
8. Hammer HB, Iagnocco A, Mathiessen A, Filippucci E, Gandjbakhch F, Kortekaas MC, Moller I, Naredo E, Wakefield RJ, Aegerter P, D'Agostino MA. Global ultrasound assessment of structural lesions in osteoarthritis: a reliability study by the OMERACT ultrasonography group on scoring cartilage and osteophytes in finger joints. Ann Rheum Dis. 2016 Feb; 75(2):402-407.
9. Mathiessen A, Haugen IK, Slatkowsky-Christensen B, Boyesen P, Kvien TK, Hammer HB. Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations with MRI, radiographs and clinical joint findings. Ann Rheum Dis. 2013 Jan; 72(1):51-56.
10. Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, Green MJ, Veale DJ, Isaacs JD, Emery P. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum. 2000 Dec; 43(12):2762-2770.
11. Moller I, Bachkaus M, Ianta J, et al. The 2017 EULAR standardised procedures for ultrasound imaging in rheumatology. Annals of Rheumatic Disease. 2017; In Press.


Participant research ID:
First and last initial:
Date:
Sonographer:
WRIST
R ECU
R IC, RC, UC
WRIST
L IC, RC, UC
R ECU
R Dig Flex 5
R MCP 5
L MCP 5
L Dig Flex 5
R Dig Flex 4
R MCP 4
L MCP 4
L Dig Flex 4
R
L
R Dig Flex 3
R MCP 3
L MCP 3
L Dig Flex 3
R Dig Flex 2
R MCP 2
L MCP 2
L Dig Flex 2
R PIP 5
L PIP 5
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R MCP 1
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R MTP 5
L MTP 5
R MTP4
R MTP3
R MTP2
R MTP1
L MTP 1
L MTP 2
L MTP 3
L MTP 4
Joint
Key
Pathology
Grade
S
Synovial hypertrophy
0,1,2,3
E
Synovial effusion
0,1,2,3
P
Power Doppler
0,1,2,3
O*
Osteophyte
0,1,2,3
Er*
Erosion
Y, N
*Optional
Tendon
Key
Pathology
Grade
S
Synovial Hypertrophy
0,1,2,3
E
Synovial effusion
Y, N
P
Power Doppler
0,1,2,3
Version 2.0
31.07.2017

Participant ID: _____ **Date:** _____

Inclusion / exclusion criteria:

Inclusion criteria:	**Yes (please tick)**	**No (please tick)**
1. Is the subject aged 18 years or more?		
If 'yes' to question 1 please continue:		
Exclusion criteria:		
2. Previous or current diagnosis of inflammatory joint disease (including crystal arthropathy).		
3. Any history of joint trauma in the last month.		
4. Fulfilling hand osteoarthritis ACR criteria[Ψ].		
5. Any clinical joint inflammation as identified by a physician.		
6. Previous or current inflammatory bowel disease.		
7. History of culture-proven enteric and/or genitourinary infection in the last month.		
8. Current or previous corticosteroids use in the last 4 weeks.		
9. Current non-steroidal anti-inflammatory use.		
If 'no' to questions 2-9, please continue to the Visual Analogue Score (VAS) below:		

Please place a vertical mark (|) on the following line to indicate how much joint pain you have had in the PAST WEEK:

NO PAIN |——————————————————————| SEVERE PAIN ⌊_____⌋ mm

If VAS score is <10/100, please continue with recruitment.

Ψ The ACR criteria for the classification of osteoarthritis of the hand
Hand pain, aching, or stiffness **and** 3 or 4 of the following features: • Hard tissue enlargement of 2 or more of 10 selected joints • Fewer than 3 swollen MCP joints • Hard tissue enlargement of 2 or more DIP joints • Deformity of 1 or more 10 selected joints *The 10 selected joints are the second and third DIP, the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands.

Participant ID: _____

First and last initial		Sex			
Age (years)		Height(cm)		Weight (kg)	

Co-morbidities (please circle)	
Skin psoriasis	Yes No
Previous joint replacement	Yes No If yes, state which joint: _____

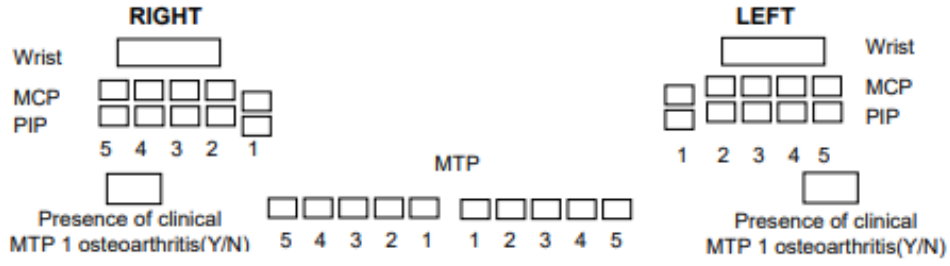
Other comorbidities; please list			

Family history (please circle)	
Osteoarthritis	Yes No
Skin psoriasis	Yes No
Inflammatory arthritis	Yes No
Connective tissue disease	Yes No
Inflammatory bowel disease	Yes No

Social history	
Hobbies involving physical activity (e.g. running, cycling, yoga, swimming, weight-lifting)	
Occupation (or last occupation if retired)	
Smoking status (please circle)	Current Ever Never
Ethnic group	

Clinical examination: Tender joint count

Mark 'T' tender "U' unable to assess
(If 'U' state reason e.g. amputation, prosthetic joint, excess peripheral oedema)



Version 2.0 31.07.2017

Appendix 2 Wrist Atlas

Wrist Grading

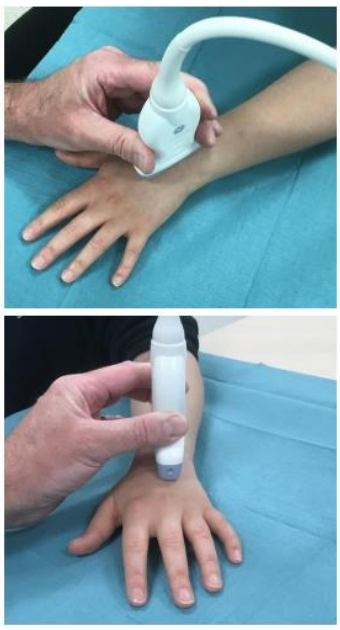
Greyscale Synovial Hypertrophy
OMERACT Minimal Disease
Ultrasound Group

V1.11 01/07/2020

Scanning approach

Neutral joint alignment, flat surface

Radiocarpal/Intercarpal view



Ulnar recess view

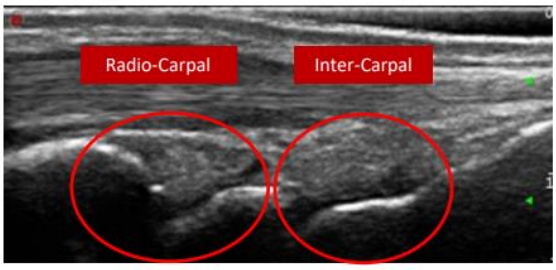
Approach to grading

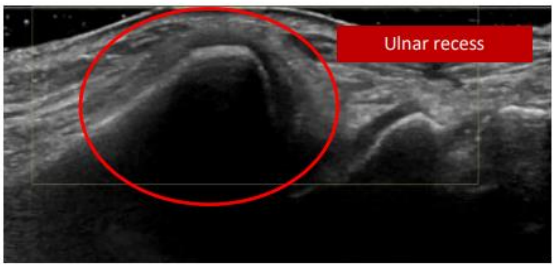
This generic approach should always be followed when using the atlas:

1. Check neutral alignment of joints
2. Identify extent of capsular/recess enlargement
3. Distinguish synovial tissue from effusion, tendon or ligamentous structures
4. Examine echogenicity of synovial tissue:
   a) hypoechoic = inflamed and should be graded
   b) iso or hyperechoic = chronic/not acutely inflamed and should not be graded
5. Compare with images in atlas to grade

Wrist scanning and alignment

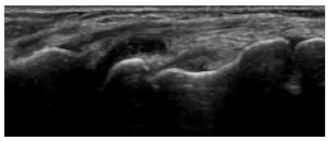
Scan long axis views of the wrist joints



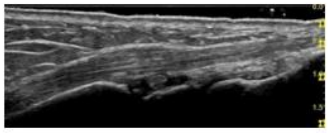


Ensure appropriate alignment of joints

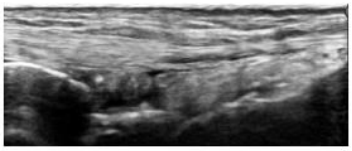
Hyperflexion



Hyperflexion



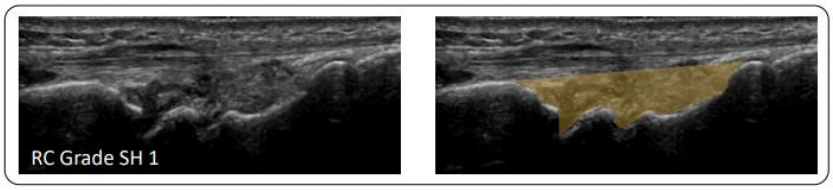
Hyperextension



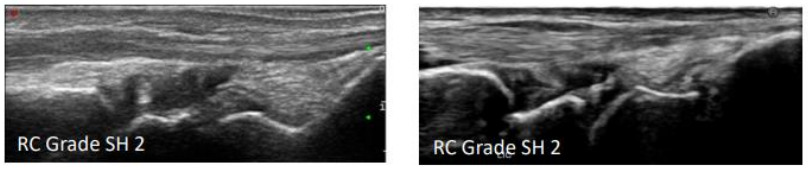
RC and IC grading

Synovial hypertrophy grading based on extent of hypoechoic synovial tissue
Grade 1 SH is demarcated by a line (shown below) joining the most superior surfaces of the distal radial and distal carpal heads

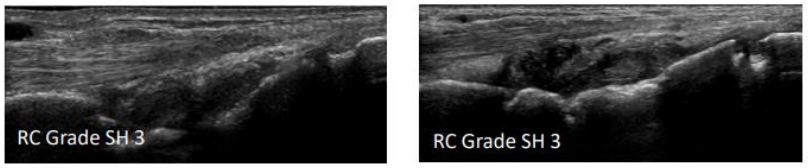
Grade 1 Minimal synovial hypertrophy: does not cross the line joining the most superior surfaces of the distal radial and distal carpal heads



Grade 2 Moderate synovial hypertrophy: graded on extent. May cross the line joining the most superior surfaces of the distal radial and distal carpal heads



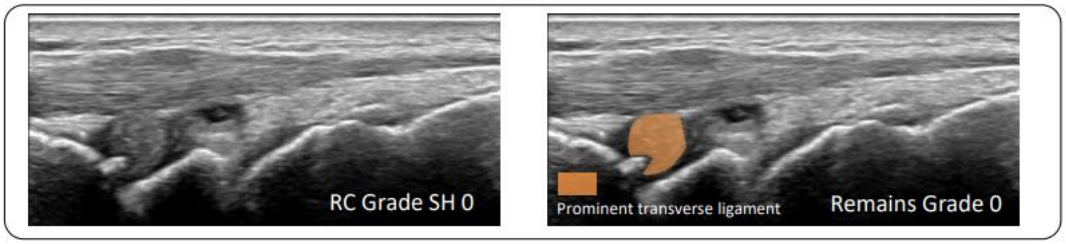
Grade 3 Severe synovial hypertrophy: graded on extent. May cross the line joining the most superior surfaces of the distal radial and distal carpal heads



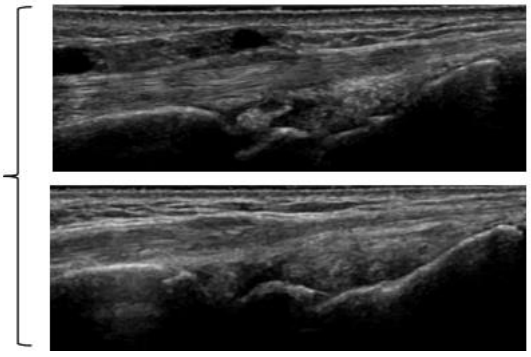
Wrist synovial recesses

Distinguish synovial tissue from effusion

Avoid confusing synovial tissue with ligamentous processes that appear to enlarge the synovial recess



Wrist RC Grade 1. Two further examples of prominent ligament structures. Only grade the extent of hypoechoic tissue

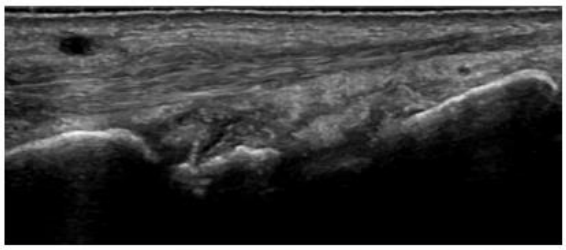


Echogenicity of synovial tissue

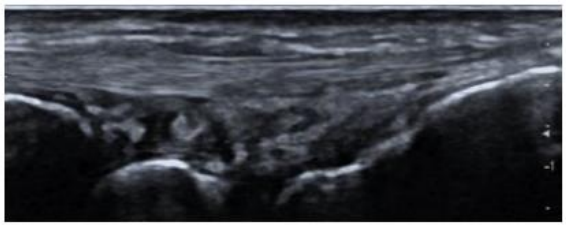
Inflamed synovial tissue is defined by hypoechogenicity

With chronicity and reduced inflammation synovial tissue may remain visible but will take on an isoechoic or hyperechoic appearance. It is important that the sonographer applies their judgement to this, and does not grade tissue that falls into this category

Wrist RC grade 0, IC grade 0, prominent hyperechoic synovium



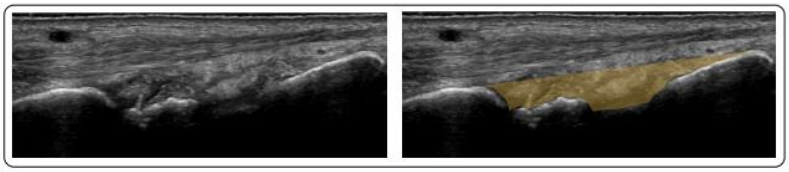
Wrist RC grade 2, IC grade 1, mixed echogenicity



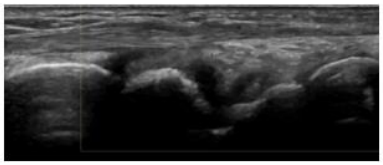
Resolving difficult gradings

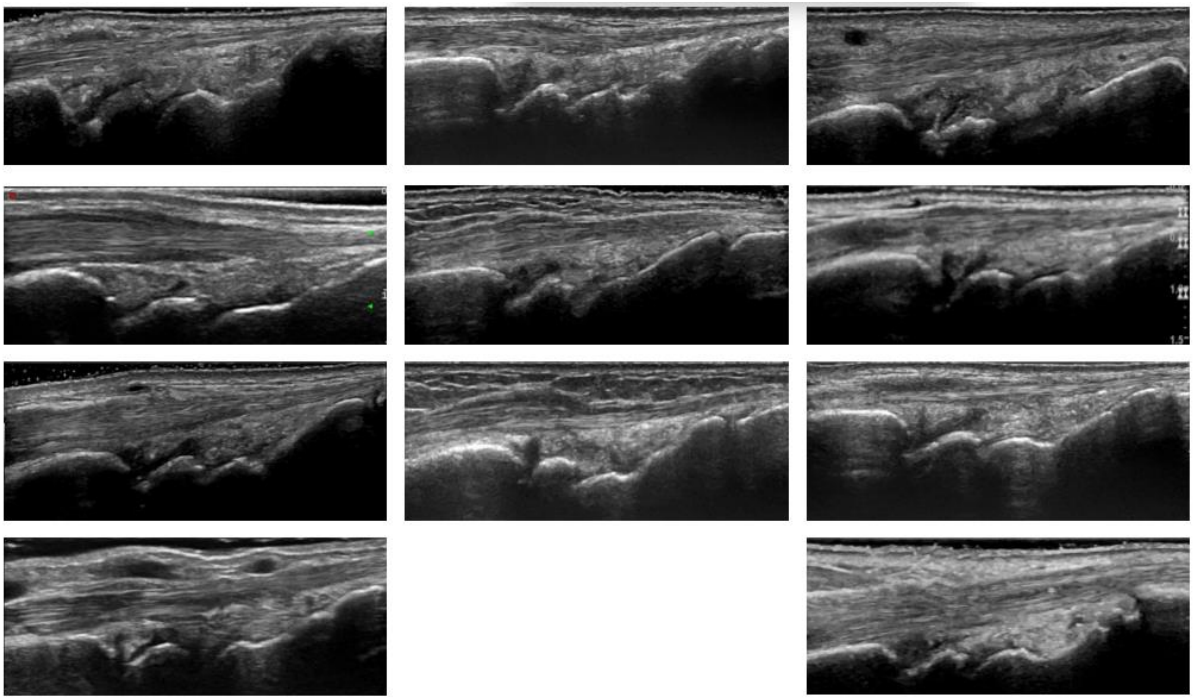
The complexity of the carpal joints can lead to variation in expansion of joint capsules. Hence multiple atlas images are shown for each grading. However some images remain difficult to grade: these have to be resolved such that the grading of synovial hypertrophy is consistent with the extent seen in atlas images

Wrist RC Grade 0. Prominent transverse ligament and hyperechoic tissue push synovial capsule above notional line. Remains Grade 0



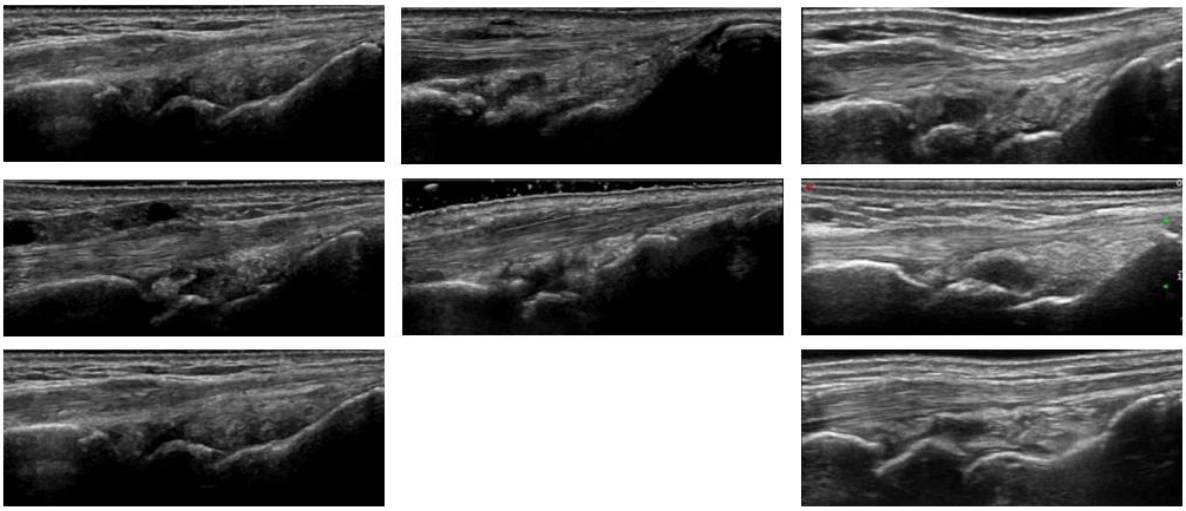
Wrist IC Grade 2. Prominent lunate profile in a correctly aligned wrist joint. IC joint extent of tissue remains Grade 2





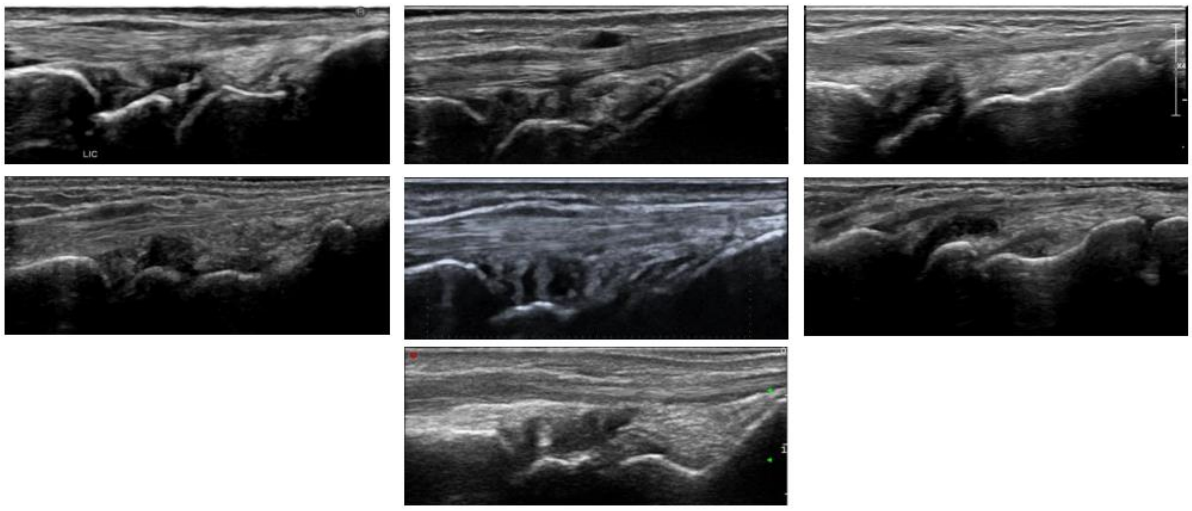
No synovial hypertrophy

Radiocarpal Grade 0



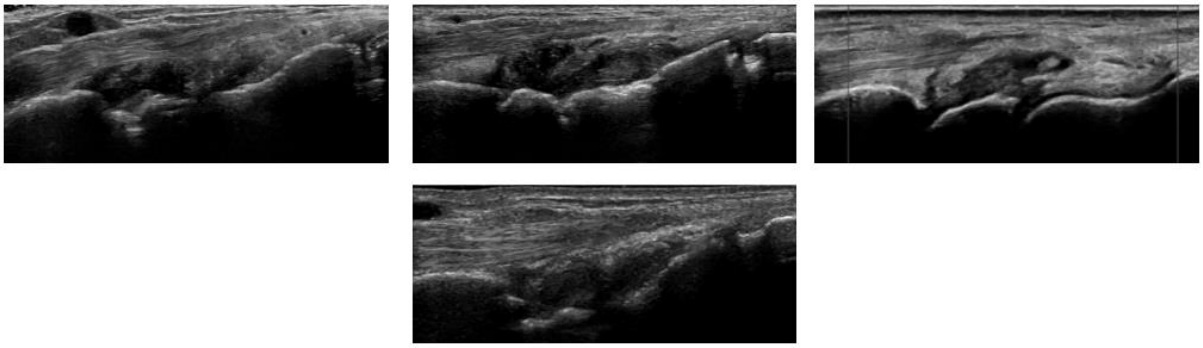
Minimal synovial hypertrophy, that does not cross a line joining the most superior surfaces of the distal radial and distal carpal heads

Radiocarpal Grade 1



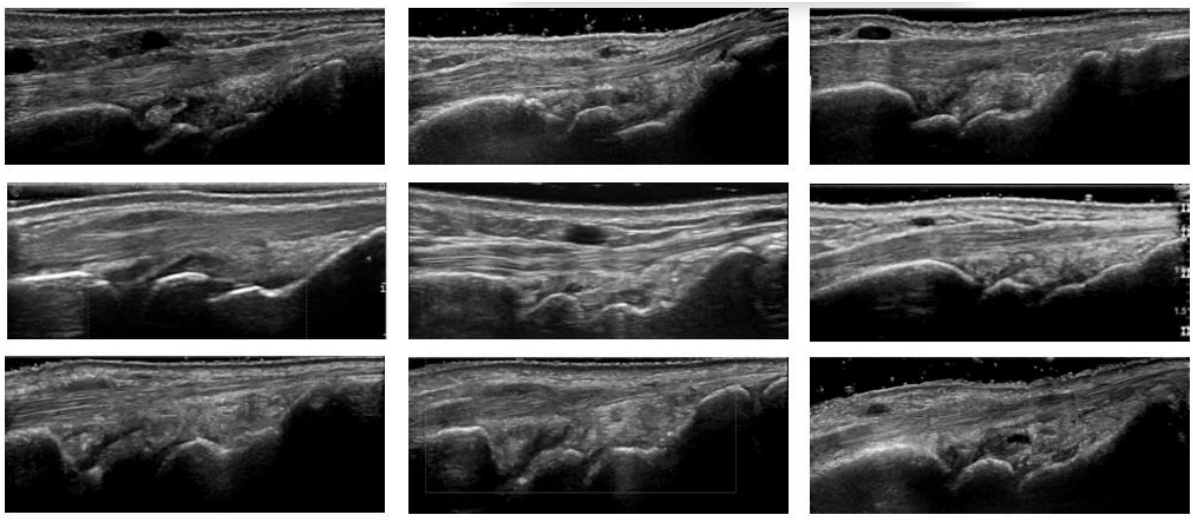
Moderate synovial hypertrophy, that may extend over a line joining the most superior surfaces of the distal radial and distal carpal heads

Radiocarpal Grade 2



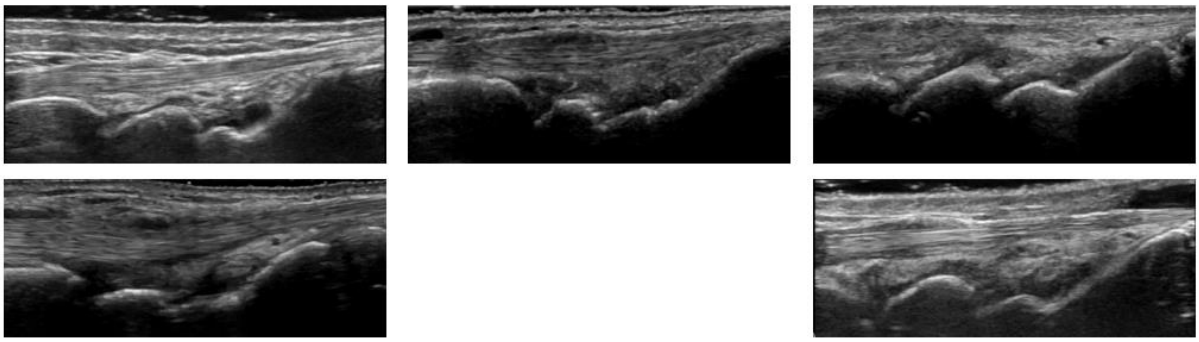
Severe synovial hypertrophy, that may extend over a line joining the most superior surfaces of the distal radial and distal carpal heads

Radiocarpal Grade 3



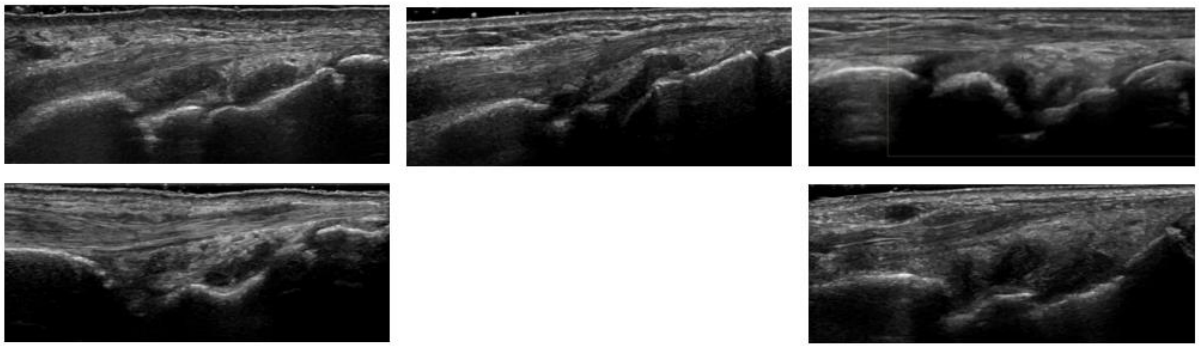
No synovial hypertrophy

Intercarpal Grade 0



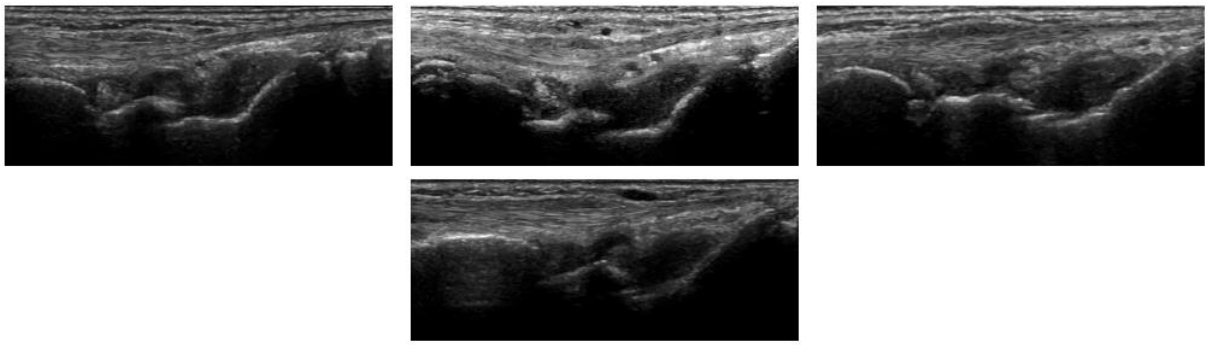
Minimal synovial hypertrophy, that does not cross a line joining the most superior surfaces of the distal radial and distal carpal heads

Intercarpal Grade 1



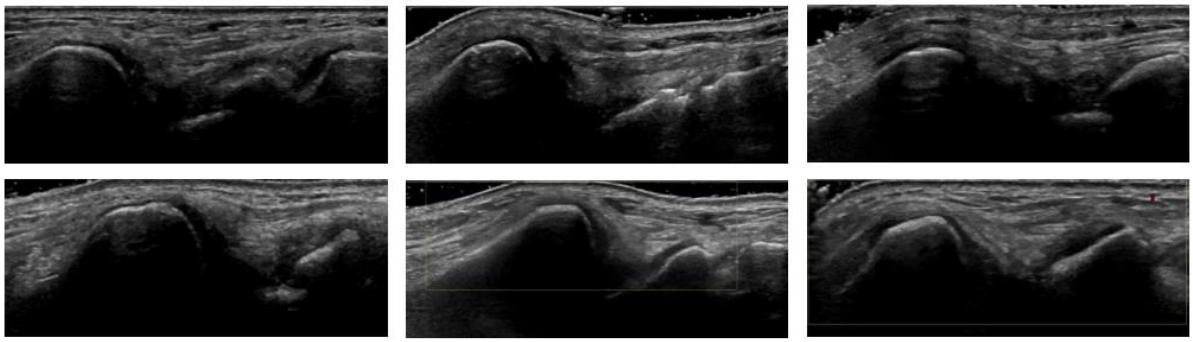
Moderate synovial hypertrophy, that may extend over a line joining the most superior surfaces of the distal radial and distal carpal heads

Intercarpal Grade 2



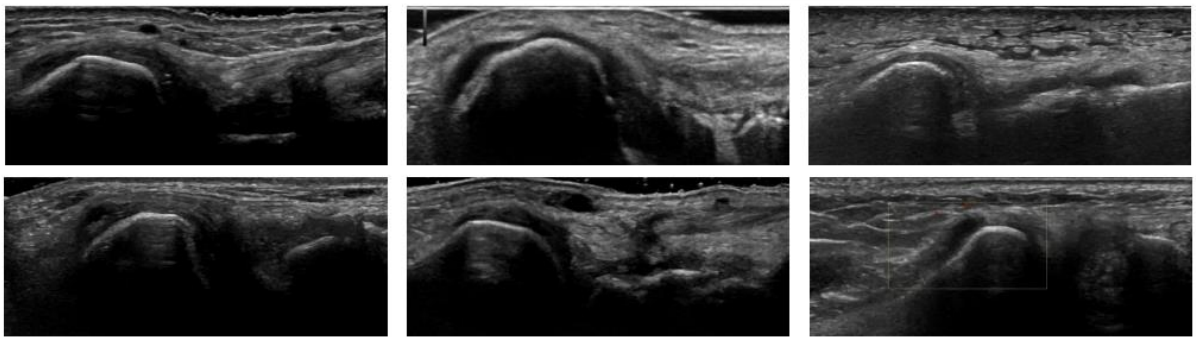
Severe synovial hypertrophy, that may extend over a line joining the most superior surfaces of the distal radial and distal carpal heads

Intercarpal Grade 3



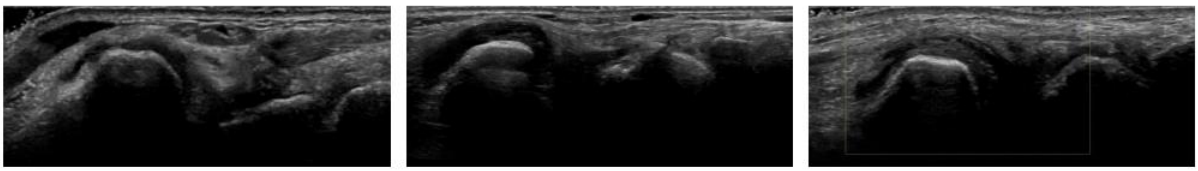
No synovial hypertrophy

Ulnar recess Grade 0



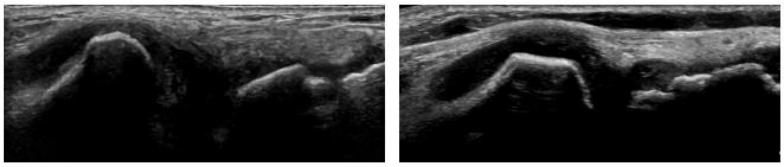
Minimal synovial hypertrophy

Ulnar recess Grade 1



Moderate synovial hypertrophy

Ulnar recess Grade 2



Severe synovial hypertrophy

Ulnar recess Grade 3

Appendix 3 MTPJ Atlas

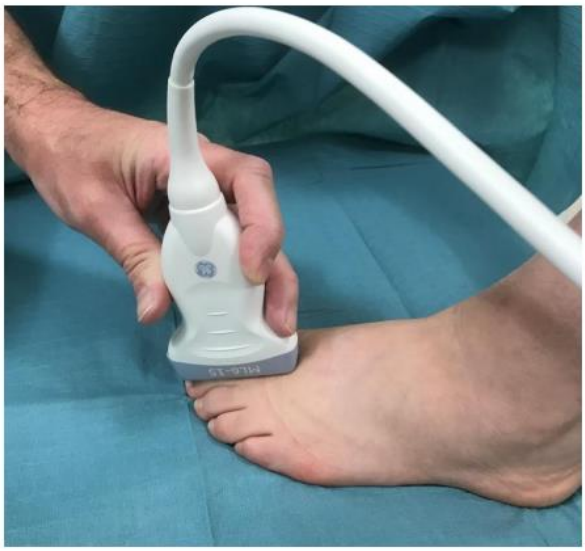
MTP Grading

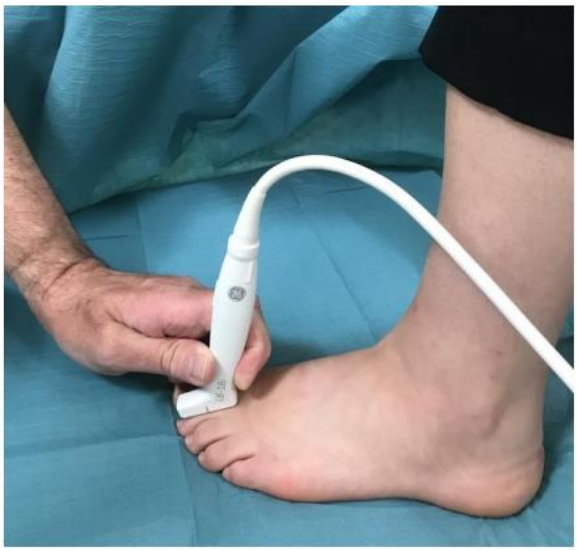
Greyscale Synovial Hypertrophy
OMERACT Minimal Disease
Ultrasound Group

V1.8 01/07/2020

Scanning approach

Scan on a flat surface with knee at 90 degrees





Approach to grading

This generic approach should always be followed when using the atlas:

1. Check neutral alignment of joint

2. Identify extent of capsular/recess enlargement

3. Distinguish synovial tissue from effusion, tendon, dorsal plate

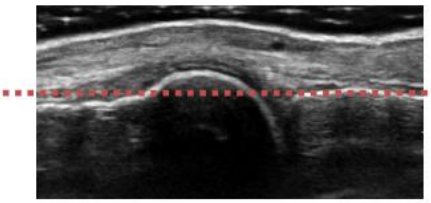
4. Examine echogenicity of synovial tissue:
   a) hypoechoic = inflamed and should be graded
   b) iso or hyperechoic = chronic/not acutely inflamed and should not be graded

5. Compare with images in atlas to grade

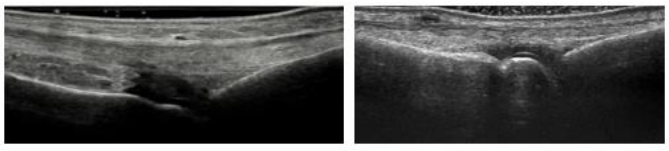
MTP alignment

Many toes are hyperextended or subluxed at the MTPJ

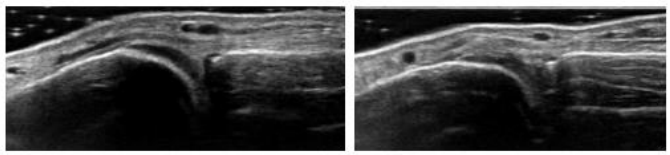
It is important to maintain a neutral position whilst scanning so that the shafts of the metatarsus and phalanx are aligned



If bones are aligned and synovial recess / effusion are compressed, these hyper-extended joints will likely become grade 0 synovial hypertrophy

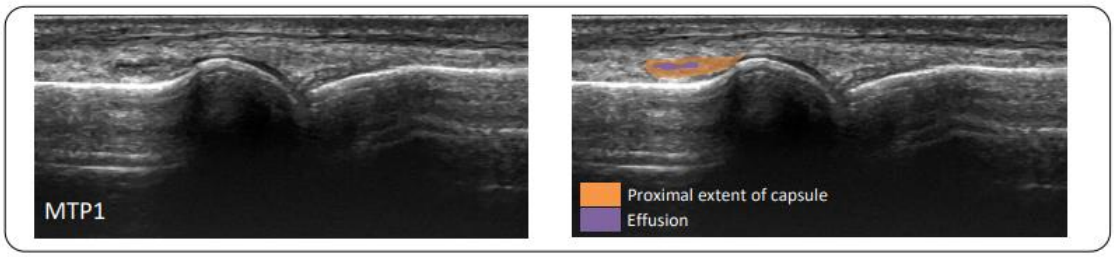


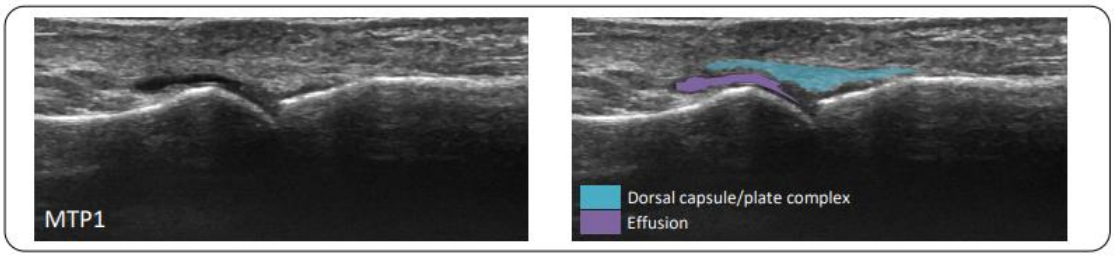
Unacceptable bone alignment due to MTP joint flexion



MTP capsule and synovial recess

Healthy MTPs have a prominent joint capsule that may extend beyond the metatarsal head along the proximal phalanx. This is often seen in the MTP1 joint. This natural joint recess is not regarded as inflammatory synovial hypertrophy for grading purposes. Joint effusion is often present in this natural recess. MTP joints, particularly MTP1, also often have a thick capsule and prominent dorsal plate. These structures should not be graded as synovial hypertrophy





Echogenicity of synovial tissue

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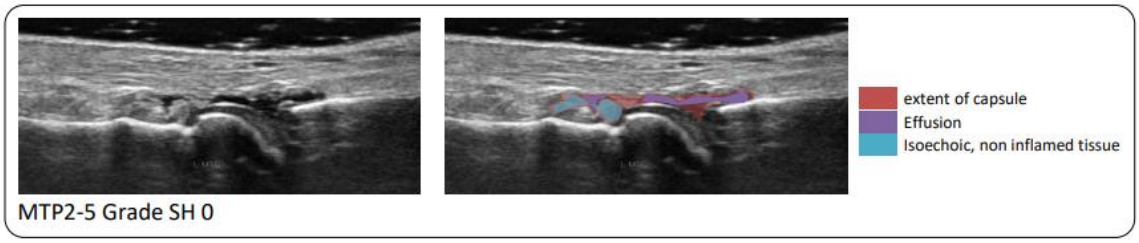
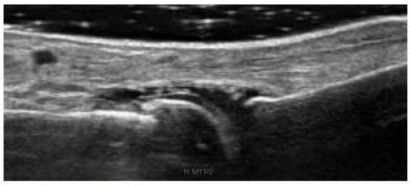
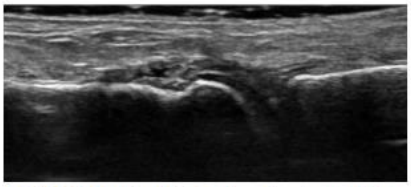
With chronicity and reduced inflammation, synovial tissue may remain visible but will take on an isoechoic or hyperechoic appearance. It is important that the sonographer applies their judgement to this, and does not grade tissue that falls into this category



MTP2-5 Grade SH 0



MTP2-5 Grade SH 0
Hyperechoic, mainly effusion



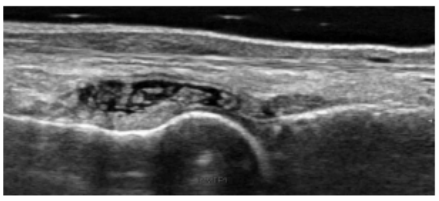
MTP2-5 Grade SH 1, mixed echogenicity

Resolving difficult gradings

Multiple atlas images are shown for each grading. However some images remain difficult to grade; example guidance is shown below

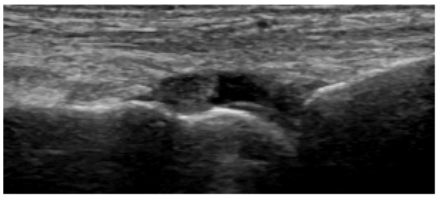
MTP1 SH Grade 2

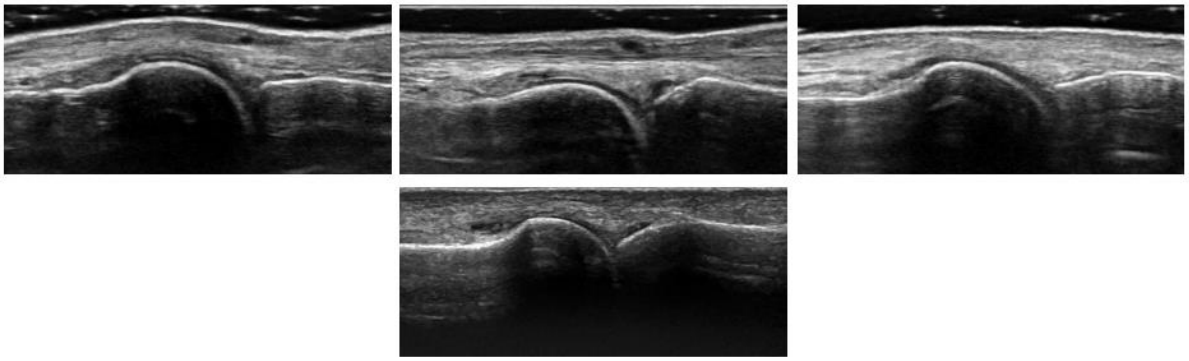
Note effusion and mixed echogenicity in both images: Only the hypoechoic tissue is graded



MTP2-5 SH Grade 1

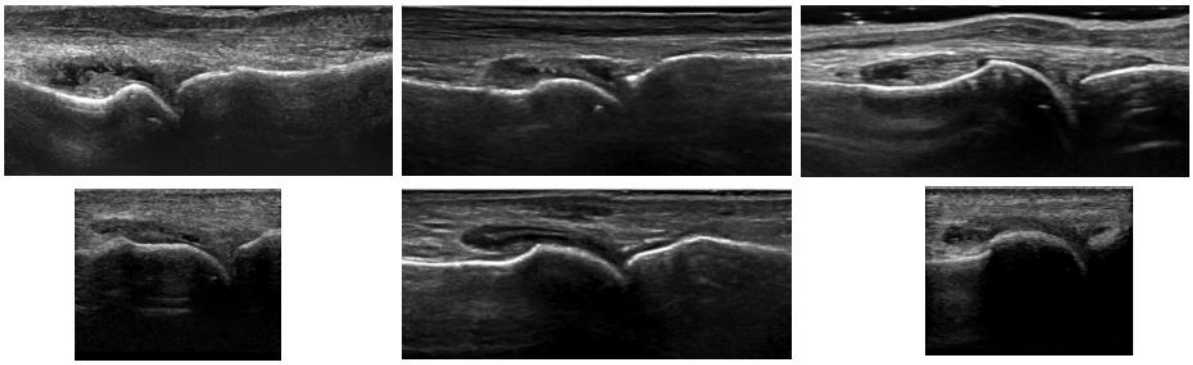
This joint is hyperextended, likely contributing to the enhanced appearance of effusion. The extent of hypoechoic synovium is Grade 1





No synovial hypertrophy

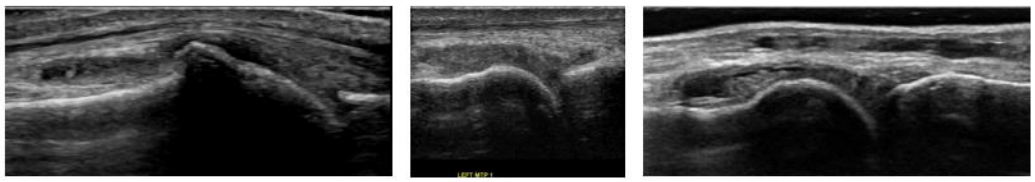
MTP 1 SH Grade 0



Minimal synovial hypertrophy

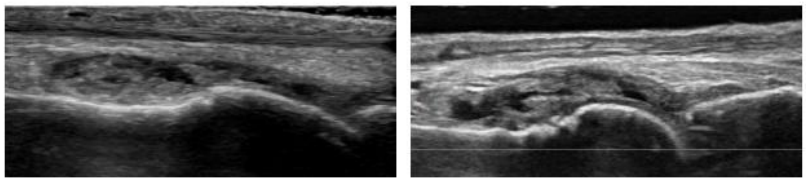
Note frequent presence of effusion within capsule

MTP 1 SH Grade 1



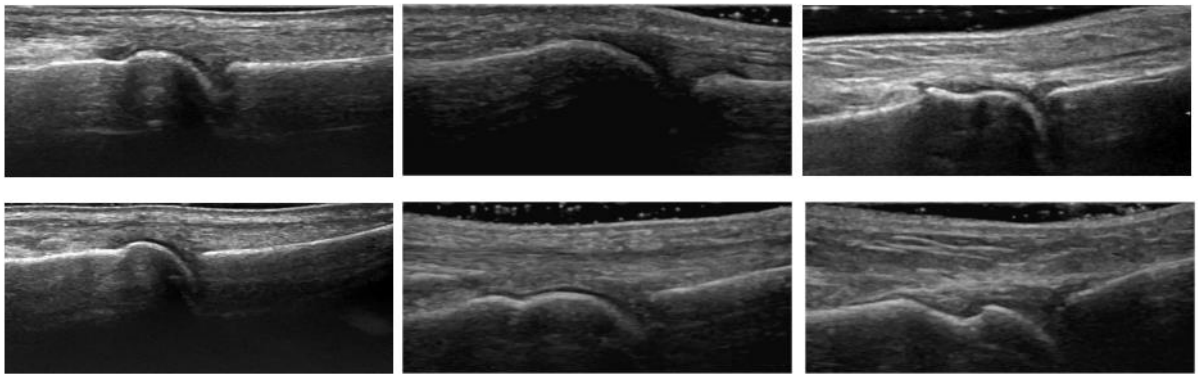
Moderate synovial hypertrophy

MTP 1 SH Grade 2



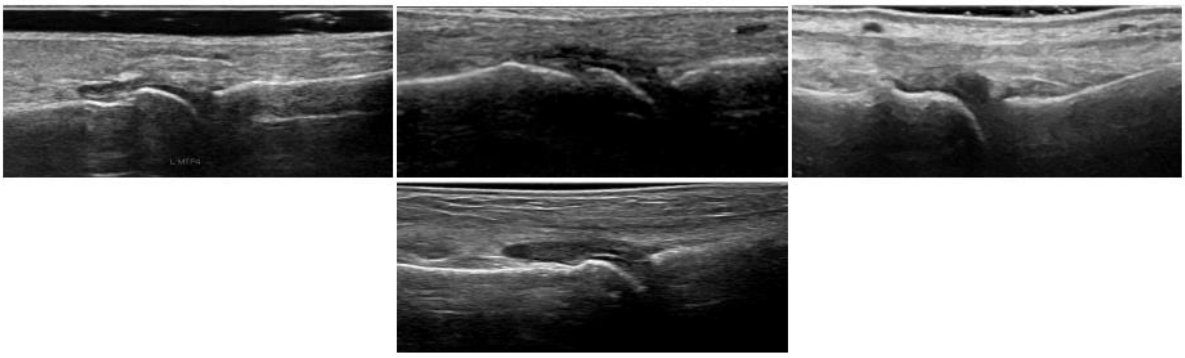
Severe synovial hypertrophy

MTP 1 SH Grade 3



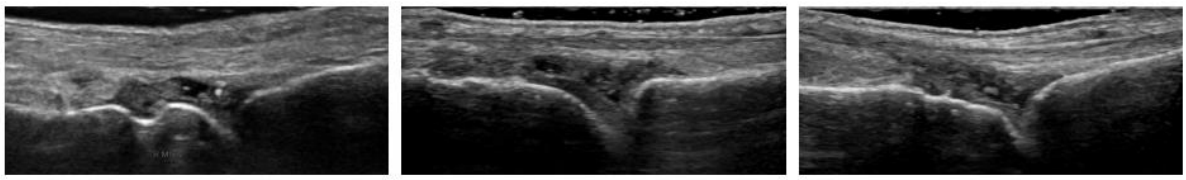
No synovial hypertrophy

MTP 2-5 SH Grade 0



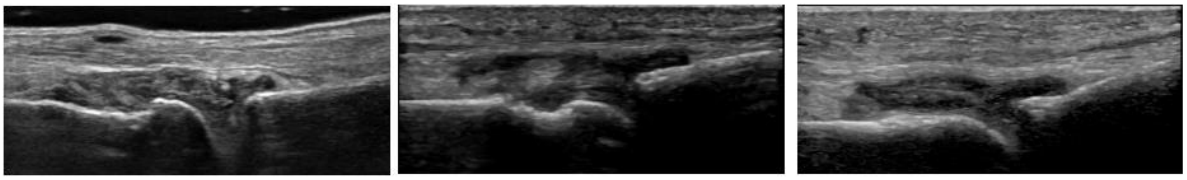
Minimal synovial hypertrophy

MTP 2-5 SH Grade 1



Moderate synovial hypertrophy

MTP 2-5 SH Grade 2



Severe synovial hypertrophy

MTP 2-5 SH Grade 3

Appendix 4 BEACON CRF

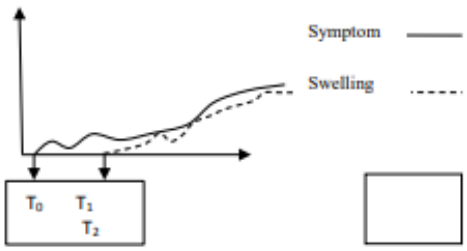
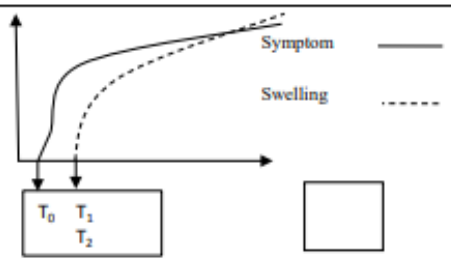
Predicting Outcome in Inflammatory Arthritis: Baseline Assessment

EAC ID:	**Sticker or Name/Reg no.**
Initials:	
Microbiome ID:	
Date:	

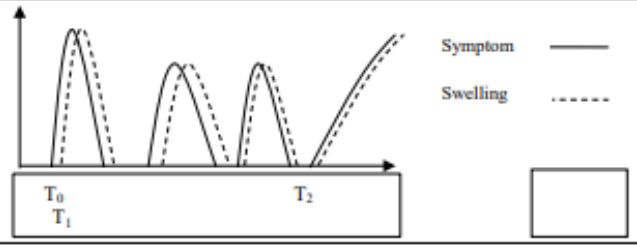
First name		**Surname**	
Date of birth		**Sex**	

Current inflammatory arthritis	**dd/mm/yr**
Onset of **current symptoms** (T_0)	_ _ / _ _ / _ _
Onset of **any related** inflammatory joint swelling (T_1)	_ _ / _ _ / _ _ , or date N/A ☐ no joint swelling ☐
Onset of **current ongoing** inflammatory joint swelling (T_2)	_ _/_ _/_ _ , or date N/A ☐ no current joint swelling ☐
Clinical pathway milestones	
Date of first assessment by first health care professional	_ _ / _ _ / _ _ or date N/A ☐
Date of referral by health care professional to rheumatology	_ _ / _ _ / _ _ or date N/A ☐
Date of first rheumatology consultation	_ _ / _ _ / _ _ or date N/A ☐
Source of referral	GP / A&E / other: specify _____
Target of referral	Early arthritis clinic / General referral
Status of referral	Urgent / routine
Additional Demographics	
Ethnic category (2001–census classification)	Select one from list on page 11
Highest educational achievement	Select one from list on page 11

Mode of onset Tick one that best describes the nature of the presentation

Insidious onset	Abrupt onset
	
Onset that begins gradually and reaches a maximum intensity within weeks or months.	Onset that begins abruptly and reaches a maximum intensity within hours or days.

Palindromic onset

	A history or physical examination findings consistent with symptoms and/or synovial swelling that returns to normal between attacks.

Synovial fluid polarised microscopy	Tick one
Not done	
Done: Negative	
Done: Urate crystals	
Done: Pyrophosphate crystals	
Done: Other crystal type	

Presenting complaint and diagnosis		
Current morning stiffness (minutes)		
Current **working diagnosis**		
Current **classified diagnosis** (doctor to complete)		
Does this patient have continuing arthralgia without synovitis?	No	Yes
Does this patient have continuing palindromic arthritis?	No	Yes

Extra-articular features		
Skin	Nodules	Ever / Never
	Psoriasis	Current / Never / Ever
	Erythema nodosum	Never / Ever
	Gouty tophi	Never / Ever
	Circinate ballanitis	Never / Ever
	Keratoderma blenorrhagica	Never / Ever
	Vasculitic rash	Never / Ever
	Other rash	Never/ free text (=ever) _____
Nails	Pitting	Never / Ever
	Onycholysis	Never / Ever
MSK	Inflammatory back pain	Current / Never / Ever If "ever", tick each option **Age of onset**: ≤45 yrs ☐ >45yrs ☐ **Duration**: ≤ 3 mths ☐ >3 mths ☐ **Radiology evidence**: None ☐ MRI only ☐ X-ray only ☐ X-ray and MRI ☐
	Enthesitis	Never / Ever
	Dactyltis	Never / Ever
	Joint replacement	Never / Ever If "ever", tick one: Trauma ☐ Current inflammatory ☐ Osteoarthritis ☐ Other ☐
Ocular	Iritis	Ever / Never
	Episcleritis	Ever / Never
	Scleritis	Ever / Never
	Sicca	Ever / Never
	Conjunctivitis	Ever / Never
GI	Preceding GI infection	Y / N
	Inflammatory bowel disease	Ever / Never
GU	Urethritis	Ever / Never
	Preceding GU infection	Y / N
	Preceding UTI	Y / N
Lungs	Pleural effusion	Ever / Never
	Pulmonary fibrosis	Ever / Never
	Bronchiectasis	Ever / Never

Past medical history and cardiovascular risk factors (circle each option)	
Angina or MI	Yes No
Coronary stents	Yes No
Congestive heart failure	Yes No
Stroke	Yes No
TIA	Yes No
Peripheral vascular disease	Yes No
Diabetes mellitus	Yes No
Hypertension	Yes No
Known hyperlipidaemia	Yes No
Family history of CVS disease	Yes No
Obesity	Yes No

Smoking and alcohol	
Smoking status	Current / Ever / Never
Age started smoking	
Age stopped smoking	
Approximate daily intake (number of cigarettes per day)	
Current alcohol intake (number of units per week)	

Other co-morbidities	Year

Family history of rheumatological disease*

*Inflammatory arthritis or connective tissue disease in first degree relatives

Condition	**Relationship**
Psoriatic arthritis in first- or second-degree relatives	Yes No

Patient completed;

For each of the following, place a vertical mark (I) on the line to indicate severity:

Patient pain

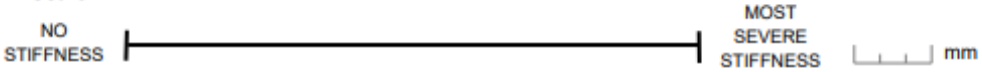
How much pain have you had because of your illness IN THE PAST WEEK?

Patient global

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale:

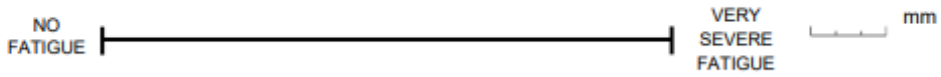
Patient early morning stiffness severity

Considering the stiffness of your joints in the morning, rate its severity on the following scale:



Patient fatigue severity

Considering the amount of fatigue you have, rate its severity on the following scale:

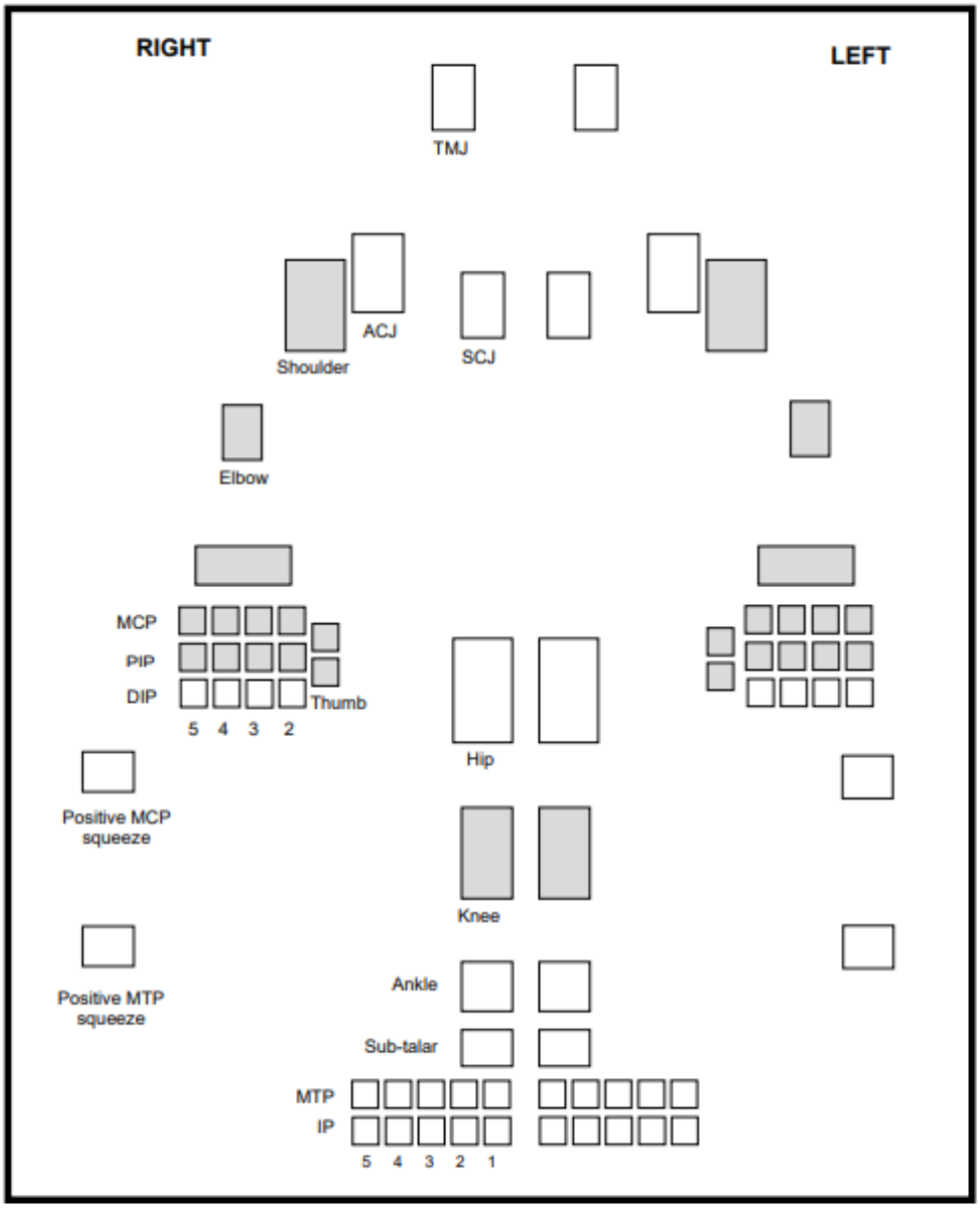


Occupation **(High level categories of the ONS Standard Occupational Classification 2010)**	**Tick one**
Managers, Directors and Senior Officials	
Professional Occupations	
Associate Professional and Technical Occupations	
Administrative and Secretarial Occupations	
Skilled Trades Occupations	
Caring, Leisure and Other Service Occupations	
Sales and Customer Service Occupations	
Process, Plant and Machine Operatives	
Elementary Occupations	
Employment status	**Tick one**
Working (employed)	
Working (employed)	
Working (self-employed)	
Retired (planned)	
Unemployed	
Never worked	
Off work due to inflammatory arthritis	
Off work due to other illness	
Retired due to inflammatory arthritis	
Retired due to other illness	
Student	
Homemaker	

Assessor's global disease activity

ARTHRITIS INACTIVE ——————— ARTHRITIS VERY ACTIVE _____ mm

Tender joint count (68) & swollen joint count (66 - hips excluded):
Mark 'T' tender 'S' swollen 'B' both 'U' unable to assess
(Give reason e.g. amputation, prosthetic joint, excess peripheral oedema)



General examination				
Height (cm)			Waist circumference (cm)	
Weight (kg)			Hip circumference (cm)	
Systolic BP (mm Hg)			Thigh circumference (cm)	
Diastolic BP (mm Hg)				
Urine dipstick abnormalities (state results)	Protein		Leucocytes	
	Nitrites		Glucose	
	Blood			

Medications prior to first visit

One off Steroid therapy		
Intramuscular steroid injection	No Yes	How many? _____
Intraarticular steroid injection	No Yes	How many? _____
One-off course of oral steroids	No Yes If yes, how many days? _____	

Type	Name	Maximum stable dose*	Date started	Date finished
DMARDs			__/__/__	__/__/__
			__/__/__	__/__/__
Continuous oral Steroids			__/__/__	__/__/__
Biologics			__/__/__	__/__/__
NSAIDs				

Other drugs taken by the patient – name only		

* mg /day or /week for MTX

Laboratory tests & samples (Tick when ordered)

Biochemistry		Haematology		Immunology	
Uric acid		FBC		Rh Factor	
Total and HDL cholesterol		ESR		anti-CCP	
Glucose				ANA	
HbA_{1c}					
CRP					
Vitamin D		**Serology**			
TSH		Parvovirus serology (Only if symptom duration less than 6 months)			

Research assessments (Tick when obtained)

Sample	Tick
10-12 mls serum: 2(SWBH) / 3(UHB) yellow top tubes with clot activator	
EDTA blood: 2 x 4 ml tube (one for plasma and one for genetics)	
PAX gene tube x 1	
Additional blood samples according to local protocol	
Random urine	
Joint ultrasound	
Plain radiographs of hand and foot	Place: _____ Date: _____

Questionnaires (Tick when obtained)

Baseline	Tick	1*,2*,3*,4*,6M	Tick	Annual	Tick
EQ-5D-5L		EQ-5D-5L		EQ-5D-5L	
WPAI: RA		WPAI:RA		WPAI: RA	
HAQ-DI		HAQ-DI		HAQ-DI	
AUDIT3				AUDIT3	
PHQ-9				PHQ-9	
FACIT-fatigue				FACIT-fatigue	
SPARRA questionnaire				SPARRA* Only for patients with ongoing inflammatory arthralgia at 12 and 24M.	
Palindromic baseline questionnaire Only for patients with palindromic-onset.				Palindromic follow-up questionnaire Only for patients with ongoing palindromic arthritis.	

*TETRA study only

Ethnic category: 2001 census classification	Highest educational achievement
White - British White - Irish White - Any other White background Mixed - White and Black Caribbean Mixed - White and Black African Mixed - White and Asian Mixed - Any other Mixed background Asian or Asian British - Indian Asian or Asian British - Pakistani Asian or Asian British - Bangladeshi Asian or Asian British - Any other Asian background Black or Black British - Caribbean Black or Black British - African Black or Black British - Any other Black background Other Ethnic Groups – Chinese Other Ethnic Groups - Any other ethnic group Not stated	No qualifications Lower Secondary education: no qualifications Lower Secondary education: O level, CSE, GCSE, Scottish Intermediates or equivalent Upper Secondary education: no qualifications Upper Secondary education: A level, Scottish Highers or equivalent Other Higher education Degree level or above

List of first degree relatives	List of second degree relatives
Mother Father Brother Sister Son Daughter	Grandfather Grandmother Uncle Aunt Nephew Niece Grandson Granddaughter

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