



**University of
Nottingham**
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**SYNOVIAL CHANGES
DETECTED BY ULTRASOUND
IN COMMUNITY-DERIVED PEOPLE
WITH KNEE PAIN**

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for the degree of Doctor of Philosophy**

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DECLARATION

I hereby declare that this thesis is result of original research. It has been conducted substantially by myself with assistance as outlined below. It has not already been accepted for any degree, diploma or other qualification. All authors and works to which reference has been made are fully acknowledged.

Study design, literature search, systematic review, application for ethics approval, recruitment, data collection (including ultrasound assessment and radiographic scoring), analysis and thesis writing were conducted primarily by myself under the supervision of Professor Weiya Zhang and Professor Michael Doherty. Dr. Michelle Hall provided support as the second reviewer for the systematic review (data extraction and quality assessment), and as the second sonographer in the baseline case-control study and in the inter-observer reliability test. Dr. Gwen S Fernandes provided support as the second x-ray reader for all studies. Nadia Frowd, Laura Marshall and Joanne Stocks performed muscle strength assessment for the case-control study. All intra- and inter-observer agreement tests (including ultrasound, radiographic and muscle strength assessment) were analysed by myself. Dr. Jonathan Moses provided support as the second reviewer for the systematic review (data extraction and quality assessment). Dr. Archan Bhattacharya provided statistical advice on multi-level modelling for the case-control study. Mrs

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ABSTRACT

Background: Knee pain, the main symptom of knee osteoarthritis (OA), affects one in 4 people aged over 55 years, of whom 10% have mild-to moderate disability. The aetiology of knee pain is heterogeneous and its relationship with structural changes and function is unclear. An important role for synovial pathology in the initiation and progression of knee OA has been emphasised. However, the normal values of synovial changes detected on ultrasound (US) in the general population and their association with knee pain in community-based people with knee pain or OA remain largely unknown.

Objectives: [1] to systematically review the literature on synovial changes detected on US in people with knee pain/OA and/or in the general population. [2] to establish the normal ranges for synovial thickness and effusion and determine an optimal cut-off associated with knee pain and radiographic osteoarthritis (ROA) in community-derived men and women over 40 years old. [3] to examine whether community-derived people with early and chronic established knee pain have different risks of having effusion, synovial hypertrophy and Power Doppler signal (PDS), and to explore whether synovial changes detected on US predict/associate with subsequent knee pain worsening. [4] to explore the role of peripheral and central risk factors of knee pain, including the role of synovial changes detected on US in different types of knee pain.

Methods: *A systematic literature search* was undertaken in Medline, EMBASE, Allied and Complementary Medicine, PubMed Web of Science, and SCOPUS databases in May 2015. Frequencies of US abnormalities in people with knee OA/pain, in the general population or asymptomatic controls were pooled using the random effects model. Publication bias and heterogeneity between studies were examined.

The source population was the Knee Pain and Related Health in the Community (KPIC, n=9506) survey in Nottingham, UK. All participants had bilateral US and radiographic examination. Synovial changes detected on US were measured by two observers (inter-observer concordance correlation was 0.8 (0.6 to 0.9) for effusion and 0.7 (0.5 to 0.9) for synovial hypertrophy). OA structural changes were measured by standardised radiographs (semi-flexed weight-bearing and flexed skyline views) using the Nottingham Line Drawing Atlas (NLDA).

A cross-sectional study comprised of 299 randomly selected adults ≥ 40 years old (147 women, 152 men). The normal range (95% quintile) for effusion and synovial hypertrophy was calculated in the healthy sample (no current knee pain and no ROA, n=163). The optimal cut-off was established using ROC curve analysis.

A case-control study compared community-derived participants with early knee pain (n=298), chronic established knee pain (n=100) and no knee pain (n=94) at baseline. 166 early knee pain participants were followed-up at one year for changes in knee pain and synovial changes detected on US. Relationships between changes in synovial changes detected on US and pain severity were examined using correlation

analysis. 255 participants with early and established knee pain replied to a one-year follow-up questionnaire. Predictors of knee pain worsening were determined using logistic regression.

Central and peripheral risk factors for knee pain were examined using participants from both the cross-sectional and case-control studies (n=736). The contribution of each was presented using ROC curves. Subgroup analysis was undertaken according to the presence/absence of ROA and widespread pain (WSP) for the association between synovial changes detected on US and knee pain. A within-person analysis in participants with unilateral knee pain was also undertaken.

Results:

Systematic review and meta-analysis: 29 studies (4720 patients) were identified from the literature. The pooled prevalence of US effusion, synovial hypertrophy and PDS in people with knee OA/pain were 51.5% (95%CI 40.2 to 62.8), 41.5% (26.3 to 57.5) and 32.7% (8.34 to 63.24), respectively, which were higher than those in the general population or asymptomatic controls (19.9% (95%CI 7.8 to 35.3), 14.5% (0 to 58.81), and 15.8% (3.08 to 35.36), respectively). People with knee OA (ACR criteria or ROA) had greater prevalence of synovial changes detected on US than people with knee pain ($p=0.037$, $p=0.010$ and $p=0.009$, respectively).

Cross-sectional study: Synovial changes detected on US were different between men and women, therefore, gender-specific reference limits were estimated. In people without KP and structural OA the normal range

for effusion was between 0 to 10.3 mm for men and between 0 to 9.8 mm for women and the normal range for synovial hypertrophy was between 0 and 6.8 mm for men and between 0 and 5.4 mm for women. The effusion cut-off able to distinguish a subgroup of people with knee pain and ROA (i.e. “symptomatic OA”) with high specificity was 8.9 mm for men and 7.8 mm for women, and for synovial hypertrophy it was 5.8 mm for men and 4.2 mm for women.

Case-control study: At baseline, effusion was associated with early (OR 2.64, 95%CI 1.57 to 4.45) and established KP (OR 5.07, 95%CI 2.74 to 9.38). Synovial hypertrophy was also associated with early (OR 5.43, 95%CI 2.12 to 13.92) and established KP (OR 13.27, 95%CI 4.97 to 35.43). However, the association with effusion diminished when adjusted for ROA. PDS was uncommon (early KP 3%, established KP 2%, controls 0%). Changes in effusion or synovial hypertrophy did not correlate with changes in KP in one year. Effusion and ROA predicted worsening of knee pain at one year (aOR 1.95, 95% CI 1.05 to 3.64, and aOR 3.52 95%CI 1.37 to 9.09, respectively).

Central versus peripheral risk factors: A number of central and peripheral risk factors associated with knee pain, including WSP, pain catastrophising, knee injury, ROA, effusion and synovial hypertrophy. Although 25% of knee pain was explained by peripheral risk factors, only 5% was explained by central risk factors. Knee pain was stratified into 4 subgroups according to ROA and WSP. The association between synovial changes detected on US and knee pain varied between subgroups, being strongest in people with isolated ROA (e.g., aOR for

hypertrophy 9.99, 95%CI 5.06 to 19.03), moderate in people with ROA plus WSP (aOR 7.24, 95%CI 3.04 to 17.25), weak in people with neither ROA nor WSP (aOR 2.25, 95%CI 1.19 to 4.22) and statistically insignificant in people with isolated WSP (aOR 2.21 95%CI 0.99 to 4.93). This was confirmed by the “one-person two knee” analysis where WSP was fully balanced between painful knees and pain-free knees. The association between synovial changes detected on US and knee pain was stronger when the knees had underlying structure OA changes.

Conclusions: Effusion and synovial hypertrophy but not PDS are common in community-derived people with knee pain. These features differ in men and women, requiring different thresholds for abnormality. Synovial changes detected on US are associated knee pain, especially in people with ROA but no WSP. However, changes in effusion and synovial hypertrophy do not correlate with changes in knee pain, and effusion but not synovial hypertrophy predicts pain progression at one year. Further study of the causality between synovial changes detected on US and structural OA, and between peripheral and central risk factors for knee pain is needed.

LIST OF PUBLICATIONS

Published Papers

1. Sarmanova, A., Hall, M., Moses, J., Doherty, M. & Zhang, W.. Synovial changes detected by ultrasound in people with knee osteoarthritis - a meta-analysis of observational studies. *Osteoarthritis Cartilage*, 2016: 24, 1376-83.
2. Sarmanova, A., Hall, M., Fernandes, G., Bhattacharya, A., Valdes, A., Walsh, A., Doherty, M. & Zhang, W.. Association between ultrasound-detected synovitis and knee pain: a population-based case-control study with both cross-sectional and follow-up data. // *submitted for publication*

Presentations at Conferences

1. UK-RIME Showcase (Manchester, October 2015): Synovial changes detected by ultrasound in community-derived people with knee pain: study design and objectives (oral and poster presentation).
2. Osteoarthritis Research Society International (OARSI) World Congress (Amsterdam, March 2016): Synovial changes detected by ultrasound in people with knee osteoarthritis – a meta-analysis of observational studies (poster presentation).
3. American College of Rheumatology (ACR) Annual Congress (Washington, November 2016): Synovial Changes Detected by Ultrasonography and Their Association with Knee Pain and Osteoarthritis: A Population-Based Case Control Study (poster presentation).
4. EULAR Annual European Congress of Rheumatology (Madrid, June 2017): Synovial Changes Detected By Ultrasonography And Their Association With Osteoarthritis-related Knee Pain: A 1-year Prospective Cohort Study (poster presentation).

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ANOVA	Analysis of variance
ANOM	Analysis of means
AMS-OA	Amsterdam Osteoarthritis
aOR	Adjusted odds ratio
AUC	Area under the curve
BMI	Body Mass Index
BML	Bone marrow lesions
CC	Chondrocalcinosis
CE-MRI	Contrast-enhanced MRI
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CRP	C-reactive protein
DS	Doppler signal
FNP	False negative probability
FPP	False positive probability
EOA	Erosive hand OA
EULAR	European league against rheumatism
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
ICC	Intra-class correlation coefficients
ICOAP	Intermittent and Constant Osteoarthritis Pain
IL	Interleukin
JSN	Joint space narrowing
JSW	Joint space width
K&L	Kellgren & Lawrence
KPIC	Knee Pain and Related Health in the Community
LDA	Logically derived line-drawing atlas
LR+	Likelihood ratio of a positive test result
LR-	Likelihood ratio of a negative test result
LSC	Least significant criterion
MCID	Minimum clinical important difference
MOST	Multicenter Osteoarthritis Study
MRI	Magnetic resonance Imaging
NHANES	The National Health and Nutrition Examination Survey

NICE	National Institute for Health and Care Excellence
NLDA	Nottingham Logically derived line-drawing atlas
NOS	Newcastle-Ottava Scale
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OR	Odds ratio
PCS	Pain Catastrophizing Scale
PD	Power Doppler
PDS	Power Doppler Signal
PDQ	Pain-DETECT questionnaire
PFJ	Patello-femoral joint
PRF	Pulse repetition frequency
PGA	Patient Global Assessment
PRC	Proportional risk contribution
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
ROA	Radiographic OA
ROC	Receiver operating characteristic
RR	Relative risk
SD	Standard deviation
TFJ	Tibio-femoral joint
TJR	Total joint replacement
TKR	Total knee replacement
TNF	Tumor necrosis factor
UK	United Kingdom
US	Ultrasound
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster Universities OA Index
WSP	Widespread pain

1. INTRODUCTION

This chapter addresses the rationale for the studies undertaken for this Ph.D. The literature on the definition, classification, epidemiology and risk factors for knee pain and knee osteoarthritis (OA) is summarised. The pathology of knee OA, including the role of inflammation and mechanisms of knee pain are discussed. Studies which have attempted to explore the imaging of structural pathology of OA with emphasis on synovial changes detected by magnetic resonance imaging (MRI) and ultrasonography (US) are reviewed in terms of the associations with knee symptoms and outcomes. The study hypothesis, aims and objectives of this Ph.D. are presented in the following chapter.

1.1. Background

OA is by far the most prevalent form of arthritis and has been conserved throughout the evolution of mankind. It can affect any synovial joint but commonly presents clinically in knees, hips, hands, feet and in the apophyseal joints of the cervical and lumbar spine. During the last 20 years OA has moved up from the 15th to the 11th highest cause of disability, which is higher than the disability from ischemic heart disease (Vos et al., 2012).

Knee pain is a clinical malady related to but not fully explained by knee OA (Hannan et al., 2000, Peat et al., 2005, Bedson et al., 2007, Hadler, 1992). Knee pain is multifactorial and may be caused predominantly by peripheral risk factors such as structural knee OA (Neogi et al., 2009,

Duncan et al., 2007), or by alteration in central pain modulatory pathways as occurs in fibromyalgia (Staud, 2011). Knee pain affects quality of life (Laslett et al., 2012), leads to disability (de Rooij et al., 2016, Cross et al., 2014) and is associated with increased mortality (Kluzek et al., 2016).

1.2. Definition of knee pain and knee osteoarthritis

Knee pain in this study differs from acute knee pain due to trauma or infection in being a troublesome chronic condition often unrelated to an obvious single cause. In middle-aged and older adults knee pain is often a symptom of knee OA (Altman et al., 1986). However, the presence of osteoarthritis changes on radiographs does not always cause symptoms (Kim et al., 2015, Guermazi et al., 2012, Spector et al., 1992, Leyland et al., 2012), and people with knee pain seek treatment for pain not osteoarthritis (Underwood, 2004). Therefore knee pain has been recognised as an important patient-centred outcome (Thielke and Unützer, 2008, Neogi, 2013, Peat et al., 2001).

There is currently no standardised definition of knee pain. O'Reilly et al. (1996) compared three definitions of knee pain with respect to determined prevalence and associations with structural change in a UK population based sample (n=4057) aged 40-79 years of age:

(A) "Have you ever had pain in or around the knee on most days for at least a month? If so, have you experienced any pain during the last year?"

(B) "Have you had pain within the last year in or around the knee that occurred on most days for at least a month?"

(C) "Have you had knee pain on most days of the last month?"

(American College of Rheumatology (ACR) criteria for knee OA).

The prevalence of knee pain for questions A, B, and C were 28.3%, 25.3%, and 19.3% respectively. Question A was the most sensitive but least specific for grade ≥ 1 osteophytes (58.7% and 59.1%), whereas question C was most specific (72.7%) but least sensitive (45.4%) for grade ≥ 1 osteophytes (O'Reilly et al., 1996).

OA is a condition confined to synovial joints and characterised by focal loss of hyaline cartilage and adjacent bone response (remodelling and marginal osteophyte) and/or associated symptoms and clinical signs (knee pain, reduced range of movement, joint deformity) (Brandt et al., 2003). The classification of knee OA is mainly based on the presence of symptoms and/or structural changes in the knee joint. **Symptomatic OA** is defined by the presence of a set of clinical and radiographic signs of OA. The diagnostic criteria summarised by the ACR (formerly American Rheumatism Association (ARA)) (Table 1-1) (Altman et al., 1986) are still the most widely used criteria for OA diagnosis (Hunter et al., 2011a, Suri et al., 2012). **Radiographic OA** (ROA) is defined by the presence of structural changes on radiographic images such as osteophytes and focal joint space narrowing (JSN) and this combination is also used for diagnosis using other imaging techniques (MRI or US).

Table 1-1. ACR classification criteria of knee OA (Altman et al., 1986)

Clinical and laboratory	Clinical and radiographic
Knee pain + At least 5 of 9: <ul style="list-style-type: none"> • Age >50 years • Stiffness < 30 minutes • Crepitus • Bony tenderness • Bony enlargements • No papabile warmth • Erythrocyte sedimentation rate (Westergen) < 40 mm/hour • Rheumatoid factor < 1:40 • Synovial fluid signs of OA (clear,viscous, or white blood cell count < 2,000/mm³) 	Knee pain + At least 1 of 3: <ul style="list-style-type: none"> • Age >50 years • Stiffness < 30 minutes • Crepitus + Osteophytes

According to the latest European League Against Rheumatism (EULAR) evidence-based recommendations for the diagnosis of OA the combination of six symptoms and signs present in adults aged ≥ 40 years (persistent knee pain, limited morning stiffness and reduced function; crepitus, restricted movement and bony enlargement) corresponds with the estimated probability of having radiographic knee OA equal to 99% (Zhang et al., 2010a).

The main limitation of current accepted diagnostic criteria is low sensitivity to early changes (Kraus et al., 2015). The majority of people with knee OA have advanced and probably irreversible structural changes by the time they are clinically diagnosed (Felson and Hodgson, 2014). Several attempts have been made to define early OA with an increased focus on early structural changes which are not evident on plain radiographs. For example, Luyten et al. (2012) have recently

proposed new criteria of early knee OA (Table 1-2). Although this definition has not been validated and is not widely accepted, shifting research priority towards identifying early OA is essential for future disease modifying treatment which could be beneficial at an early stage but probably less effective at later stages of OA (Cooper et al., 2013, Guermazi et al., 2013).

Table 1-2. Criteria for early OA according to Luyten et al. (2012) (permission granted)

	Criteria	Definition
1	Knee pain	At least two episodes of pain for >10 days in the last year
2	Standard radiographs	Kellgren–Lawrence grade 0 or I or II (osteophytes only)
3	At least one	
	• Arthroscopy	ICRS grade I-IV in at least two compartments or grade II-IV in one compartment with surrounding softening and swelling
	• MRI	At least two <ul style="list-style-type: none"> • Cartilage morphology WORMS 3–6 • Cartilage BLOKS grade 2 and 3 • Meniscus BLOKS grade 3 and 4 • BMLs WORMS 2 and 3

Note: A patient can be classified as having early osteoarthritis of the knee based on clinical and imaging findings and should fulfil the following three criteria.

WORMS - Whole-Organ Magnetic Resonance Imaging Score; BLOKS - Boston Leeds Osteoarthritis Knee Score; BMLs – bone marrow lesions.

1.3. Epidemiology

The following section reviews the estimated incidence and prevalence of knee pain and OA in the general population and outlines risk factors for developing pain/OA in the knee.

1.3.1. Prevalence and incidence

The prevalence of both knee OA and knee pain in older adults is relatively high with wide variability between studies influenced by knee pain/OA definition, selection criteria, study population and other factors.

Incidence of knee pain. The annual incidence of knee pain defined as ‘pain around the knee for most days of at least a month’ was 32 per 1000 person-years (3.2% per year) in people over the age of 40 years old in a UK study by Ingham et al. (2011a). In another UK study by Jinks et al. (2008) the overall incidence of severe knee pain defined as the presence of severe pain or physical functioning limitation on the WOMAC in people over the age of 50 years old was 7% over 3 years.

Prevalence of knee pain. Two systematic reviews reported that the prevalence of knee pain varies from 6% to 63.4% (Fejer and Ruhe, 2012, Peat et al., 2001). According to two longitudinal population-based studies in the USA (the National Health and Nutrition Examination Survey (NHANES) and the Framingham study), the prevalence of knee pain was increasing in the last two decades of the studies (Nguyen et al., 2011). For example, with adjustment for both age and body mass index (BMI)

the prevalence of knee pain increased by 65% from 1974 to 1994 in the NHANES study and doubled from 1983 to 2002 in the Framingham study.

Incidence of knee OA. The estimated incidence of symptomatic knee OA among adults aged 55–64 years ranged from 0.37% to 1.02% per year depending on gender and obesity in a study by Losina et al. (2013). The incidence of symptomatic knee OA identified as all new cases who sought medical help was reported by Wilson et al. (1990) as 163.8 per 100,000 person-years. A higher rate of symptomatic knee OA at 240 per 100,000 person-years was found in members of a health maintenance organization (Oliveria et al., 1995). The estimated mean age of symptomatic knee OA diagnosis (\pm standard deviation (SD)) was 53.5 ± 14.4 years (Losina et al., 2013).

Prevalence of knee OA. The reported prevalence of knee OA also ranges widely between 6.3% and 70.8% with a pooled prevalence estimation (including symptomatic, radiographic and self-reported definition) across the population-based studies of 23.7% (95% confidence intervals (CI) 23.4 to 24) (Pereira et al., 2011). The overall prevalence of ROA (range from 6.5% to 70.8) is higher than symptomatic OA (from 5.4% to 24.2) (Pereira et al., 2011). The Framingham OA study showed that during its last 20 years the age- and BMI-adjusted prevalence of symptomatic knee OA approximately doubled in women and tripled in men, but this trend was not observed in the prevalence of knee ROA (Nguyen et al., 2011).

1.3.2. Risk factors

It is well recognised that development and progression of both knee pain and knee OA are influenced by a combination of risk factors. Generally, risk factors can be classified as either systemic or local-mechanical. Systemic risk factors reflect a generalised susceptibility to the disease, whereas local factors refer to the local joint environment. Local factors can be divided further into extrinsic (environmental factors acting on the joint such as trauma) and intrinsic risk factors (factors in the local joint environment) (Felson, 2003).

There is strong evidence to support an association between knee OA onset and increasing age, female gender, heritability, obesity, past knee injury, and quadriceps weakness (Silverwood et al., 2015, Blagojevic et al., 2010, Muthuri et al., 2011a, Zhou et al., 2014, Muthuri et al., 2011b, Richmond et al., 2013, Oiestad et al., 2015, Neame et al., 2004, Valdes et al., 2008). Moderate evidence supports occupational physical activity as a risk factor for knee OA development (McWilliams et al., 2011, Blagojevic et al., 2010). Conflicting evidence exists for nodal hand OA, constitutional knee mal-alignment and comorbidities such as hypertension or ischaemic heart disease (Silverwood et al., 2015, Brouwer et al., 2007, Hunter et al., 2007, Hayashi et al., 2012). Pattern three 2D:4D finger ratio (index to ring finger length ratio measured on hand radiographs) was reported to be a risk factor for symptomatic OA, ROA and total knee replacement (TKR) (Zhang et al., 2008, Ferraro et al., 2010, de Kruijf et al., 2014). A possible explanation for this association is prenatal androgen exposure which influences the

development of the skeleton, and may contribute to a susceptibility of cartilage to OA later in life (Brown et al., 2002, Lutchmaya et al., 2004). Moreover, symptomatic knee OA is a chronic pain condition in which pain perception can be triggered and modulated by the central nervous system. Several factors such as depression, anxiety, and widespread pain (WSP) have been shown to play an important role in development of knee pain and symptomatic knee OA (Blagojevic et al., 2010, Jinks et al., 2008, Phyomaung et al., 2014, Bastick et al., 2015, Muraki et al., 2012).

The progression of knee OA is usually slow but shows a high variability between individuals. Whereas, some people with knee OA experience a rapid progression and come to joint surgery relatively quickly, others can remain stable for many years or show improvement of symptoms. The radiographic deterioration occurs in one-third to two-thirds of individuals with OA (Arden and Nevitt, 2006). Therefore, many studies have focused on risk factors or predictors for OA progression. Risk factors for the progression of knee OA may differ from risk factors for its development. The association also depends on the definition of progression (pain worsening, function limitation, or structural progression). For example, gender and major knee injury are well-known risk factors for knee OA onset but not for progression. Current data on risk factors for incidence and progression of knee OA are summarised in Figure 1-1.

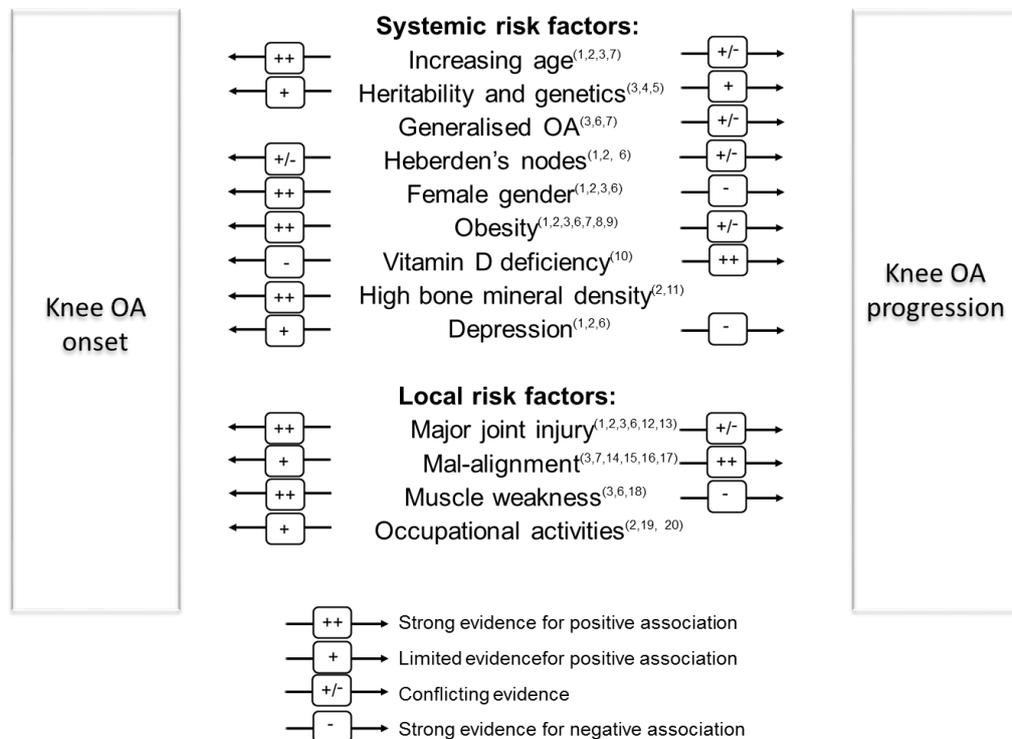


Figure 1-1. Systemic/local risk factors for development and progression of knee osteoarthritis

References: 1 - Silverwood et al. (2015), 2 - Blagojevic et al. (2010), 3 - Bastick et al. (2015), 4 - Neame et al. (2004), 5 - Valdes et al. (2008), 6 - Belo et al. (2007), 7 - Chapple et al. (2011), 8 - Muthuri et al. (2011a), 9 - Zhou et al. (2014), 10 - Cao et al. (2013), 11 - Hardcastle et al. (2015), 12 - Muthuri et al. (2011b), 13 - Richmond et al. (2013), 14 - Brouwer et al. (2007), 15 - Hunter et al. (2007), 16 - Hayashi et al. (2012), 17 - Tanamas et al. (2009) 18 - Oiestad et al. (2015), 19 - McWilliams et al. (2011), 20 - Schouten et al. (1992).

The existing studies suggest that OA is a multifactorial rather than single cause disease, and an interplay between local mechanic factors in the joint and systemic vulnerabilities determines the risk of developing the condition and its severity. For example, considering age as a factor bringing together multiple local vulnerabilities, the susceptibility of the joint to disease increases over time. The complex and overlapping system of intra- and extra-articular tissues protects joints when people are young, but with increasing age muscle weakness, knee ligament injury, and metabolic changes may lead to uneven distribution of loading and subsequent damage (Bijlsma et al., 2011, Felson, 2013). Therefore, the same risk factors such as trauma or obesity can play a different role in different age groups (Roos et al., 1995, Felson, 2013). Genetic predisposition can also range from a mal-shaped or mal-aligned joint to insufficient cartilage repair potential which in combination with other factors may lead to OA (Felson, 2004b). Therefore, the different degrees of risk and protective factors and different interactions between them result in marked heterogeneity of clinical presentations and outcomes (Brandt et al., 2003, Pritzker, 2003).

1.4. Structural pathology and pain mechanisms

The following section provides an overview of the structure of the knee joint and pathology of OA, including synovial changes, and describes the role of biomechanics, inflammation, peripheral and central mechanisms of pain in people with OA.

1.4.1. Knee joint structures

The knee is a complex synovial joint comprising three bones; the femur, patella and tibia. These bones form two articulations: the tibio-femoral joint (TFJ) and the patello-femoral joint (PFJ). The bony ends of the femur, tibia and posterior surface of the patella are covered by articular hyaline cartilage which helps cushion the articulation (Hochberg et al., 2008, Brandt et al., 2003, Pritzker, 2003). In addition to the articular cartilage, other non-osseous tissues in the knee include the menisci, collateral and cruciate ligaments, bursae, tendons, and muscles. These structures provide stability and help to resist shearing forces (Flandry and Hommel, 2011).

The TFJ is a bicondylar joint between the distal femur and proximal tibia. The tibial condyles are lined by discs of fibrocartilaginous menisci that aid joint loading and improve congruity of the joint surfaces. Collateral ligaments connect the lateral and medial condyles of the tibia and femur providing stability (Flandry and Hommel, 2011). The anterior and posterior cruciate ligaments connect the tibia and femur and play a key

role in anterior tibial translation and rotational loading (Hochberg et al., 2008).

The TFJ is covered by synovial capsule composed of fibrous connective tissue lined with the synovium. The outer fibrous layer is continuous with periosteum at its attachment to the bone (Lafeber F. et al., 2016). The inner soft tissue layer, synovium, is comprised of a continuous surface layer of cells (intima) and the underlying tissue (subintima) with a small amount of fluid between the intimal surfaces. The subintima contains blood and lymphatic vessels (Smith, 2011). The inner intima is in direct contact with the intra-articular cavity and consists of synovial cells (synoviocytes) that are subdivided into macrophages and fibroblast-like cells (type A and type B synoviocytes, respectively) (Lafeber F. et al., 2016). Macrophages are involved in removal of waste products from the synovial cavity as a result of tissue turnover. Fibroblast-like synoviocytes are mesenchymal cells involved in the production of hyaluronan (hyaluronic acid) and lubricin (e.g. proteoglycan 4). These molecules are then released into the intra-articular synovial fluid. The articular cartilage and synovial membrane are structures providing a deformable packing that reduces friction and allows a smooth and autonomous gliding of adjacent relatively non-deformable tissues as well as providing nutrition to the more superficial cartilage (Lafeber F. et al., 2016).

The PFJ is formed between the trochlea of the anterior aspect of the distal femur (femoral sulcus) and the V-shaped articular facet of the patella. The patella, or knee cap, is embedded in the quadriceps and

patellar tendon attached to the femur and tibia. The role of the patella is to provide support and to lessen the stress on the quadriceps and patella tendons during contraction of the quadriceps muscle, as well as increasing mechanical efficiency by keeping the extensor system proud of the femur (Bianchi and Martinoli, 2007).

1.4.2. Pathology of knee osteoarthritis

Under normal conditions all tissues that constitute the knee joint aim to resist mechanical forces and loading. The articular surfaces are covered by hyaline cartilage which protects the underlining bone from mechanical insults. Cartilage is viscoelastic, so it deforms with loading to maximise the contact area and minimise stress within the cartilage matrix. The loading shock is also absorbed by the subchondral bone and the periarticular soft tissues, especially muscle. Muscles play a prominent role in stabilising joint movements and loading and also serve as a protective band (Flandry and Hommel, 2011). However, when joint insult is significant or minor injuries are repetitive, this complex and overlapping system of intra- and extra-articular tissues cannot effectively protect the joint and a number of regenerative, reparative and degenerative processes occur in all tissues of the joint (Doherty et al., 2016). These early changes may result in healing or restoration of pathologic changes in the case of adequate repair and regeneration, or alternatively inappropriate repair or continuing insult might lead to non-reversible progressive tissue changes and functional failure of the joint (Bijlsma et al., 2011, Felson, 2013).

OA affects all joint tissues and typically is characterised by focal cartilage loss, osteophyte formation, subchondral bone remodelling, and synovial and capsular thickening (Scanzello and Goldring, 2012, Guermazi et al., 2013, Brandt et al., 2006) (Figure 1-2). At the early stage the hyaline cartilage responds to insult by hyperhydration or edema of superficial and middle zones, which become softer and thinner. Chondrocytes increase

their numbers to form clones or nests of cells and produce more proteoglycans and other matrix components, taking on a hypertrophic phenotype which is highly characteristic of OA. Subchondral bone reacts to insult by activation of the osteoclast-osteoblast system which leads to bone resorption and incremental bone formation. The density of the

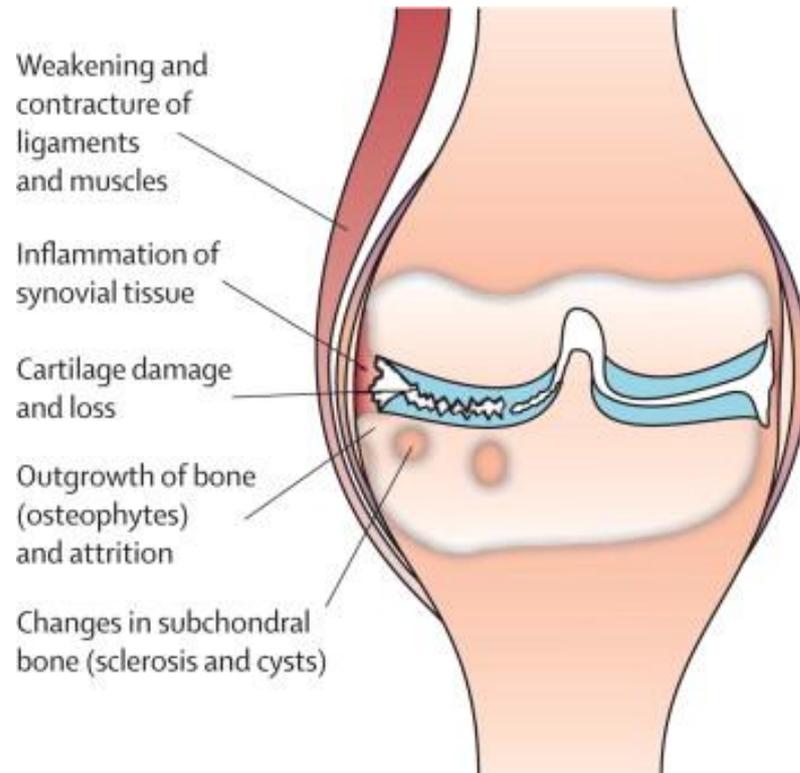


Figure 1-2. Schematic drawing of changes in different tissues of the osteoarthritic joint

Note: Image reproduced with permission of the rights holder. Original image could be found: *Bijlsma et al.(2011)*.

subchondral bone which normally is viscoelastic changes and becomes less resilient to loading. The calcified cartilage is penetrated by blood vessels and the advanced tidemark (the junction between calcified and non-calcified cartilage) moves towards the joint space (Doherty et al., 2016).

Synovial reaction presents by activation and proliferation of synovial lining cells, and infiltration of inflammatory cells into the sublining tissue. Even at the early stage these changes contribute to the thickening (hyperplasia) of the synovial membrane and to slender villous formation (Lafeber F. et al., 2016). Cytokines stimulate secretion of extra fluid and joint effusion represents one of the earliest clinical signs of synovial pathology within the knee joint. Mononuclear activation (e.g. macrophages and T cells) leads to the production of angiogenic factors, chemokines, pro-inflammatory mediators, and proteases resulting in increased synovial inflammation and tissue destruction. Angiogenesis (neo-vascularisation) plays an important role in potentiating inflammatory pathways and in transition from acute to chronic synovitis (Lafeber F. et al., 2016). Intracapsular, extrasynovial-located fat pads also contribute to inflammation by producing adipokines, cytokines, and other mediators (Lafeber F. et al., 2016).

The oedema and proliferative response are also seen in the intra-articular ligaments and capsule leading to fibrosis and movement limitation. Adaptation of these structures to repeated effusions may lead to joint laxity and instability. Limitation of joint movement caused by pain and the accompanying oedema of periarticular tissues result in muscle dysfunction and disuse atrophy (Doherty et al., 2016).

1.4.3. Role of biomechanics

Kellgren (1961) defined OA as “an expression of a joint's inadequacy to meet the mechanical stress placed upon it”. This definition highlights the imbalance between loading and protection as a key issue of OA pathology. There are several fundamental pathways for OA development: [1] “abnormal” loading on normal cartilage; [2] “normal” loading on abnormal cartilage; and [3] “abnormal” loading on abnormal cartilage (Goldring and Goldring, 2010). Various combinations of risk factors could lead to tissue alteration and damage (Pritzker, 2003).

In light of the pathological concept of OA as a potential repair process, the inappropriate (exaggerated or inadequate) response of all joint tissues to mechanical stress with “secondary” inflammation following the tissue injury and abnormal patho-mechanics plays an important role in OA development (Felson, 2013, Brandt et al., 2009). This concept explains typical OA features such as cartilage loss, subchondral bone thickening and new bone formation (Brandt et al., 2003). The cartilage loss is more prominent at the maximum load-bearing site of the joint (Segal et al., 2009, Felson, 2013, Beckwee et al., 2015). The localization of marginal osteophytes strongly associates with sites of increasing narrowing in knees (Boegard et al., 1998, van der Kraan and van den Berg, 2007). The osteophytes help to protect the joint by increasing the joint surface and joint stability (Pottenger et al., 1990, Felson et al., 2005).

1.4.4. Role of inflammation

Some degree of inflammation is commonly present in joints with OA. Tissue histology and immunohistochemistry are commonly used to detect local inflammation (synovitis) in OA joints. Microscopic assessment of synovitis shows a mild to moderate degree of inflammation in up to 50% at different stages of OA (Mathiessen and Conaghan, 2017, Rollín et al., 2008). Synovial changes at the cell level include lymphocyte and macrophage infiltration, perivascular infiltrates, synovial hyperplasia and angiogenesis (Scanzello, 2012). OA-associated synovitis can be observed at the macroscopic level on arthroscopy and usually presents as hyperplastic, inflammatory, fibrotic or detritus-rich synovial changes (Oehler et al., 2002). The first two patterns are characterised by villous or diffuse hyperplasia of synovial lining, infiltration, and increased synovial vascularity and may vary with the stage of the disease. Capsular fibrosis and cartilage and bone debris are more often observed in individuals with late-stage OA (Scanzello and Goldring, 2012). Modern imaging techniques are also able to visualise some aspects of synovitis (e.g. effusion, synovial hyperplasia, fat pad activation, hypervascularisation) (Mathiessen and Conaghan, 2017).

Although OA traditionally has been classified as a non-inflammatory arthritis, since the classical view of OA as a disease of articular cartilage shifted to consideration of OA as failure of the entire joint, the importance of systemic and local inflammation has been re-evaluated and increasingly emphasised (Driban et al., 2010, Berenbaum, 2013, Siebuhr et al., 2014, Sokolove and Lepus, 2013).

From the inflammatory perspective, it is claimed that pathological changes such as synovial lining cell hyperplasia with focal lymphocyte and monocyte infiltration, effusion and increased levels of inflammatory mediators in synovial fluid associate strongly with symptoms of pain and stiffness, especially at the knee, and that inflammation is a key determinant of structural and patient-centred outcomes (Sokolove and Lepus, 2013, Berenbaum, 2013). Certainly, knee warmth and early morning stiffness in people with knee OA appear to associate with radiographic progression (Ledingham et al., 1995, Mazzuca et al., 2006). More convincingly, effusion-synovitis and Hoffa-synovitis detected by MRI associate with incident radiographic knee OA after 1-year (Atukorala et al., 2016). Inflammatory signs observed in synovium by arthroscopy of people with symptomatic medial tibiofemoral OA also associate with progression of chondropathy and pain on a Visual Analogue Scale (VAS) after one-year (Ayril et al., 2005). Moreover, in people with OA the synovial fluid leukocyte count associated with greater pain reduction after steroid injection (McCabe et al., 2017). According to a systematic review, strong evidence supports the link between increased serum markers of systemic inflammation (tumor necrosis factor alpha (TNF- α), hyaluronic acid level and ultrasensitive CRP) and OA (Jin et al., 2015).

However, despite this evidence the question as to whether episodes of inflammation in OA are triggered by mechanical insult or arise spontaneously with the slow pathological process of the disease remains unclear. Firstly, although the natural history of OA often includes periods of increased pain, morning stiffness, joint tenderness, effusion, and

activity limitation known as “flare-ups” or “flares”, these symptoms are usually benign and resolve quickly (Kittelson et al., 2014). Furthermore, pathological changes associated with inflammation in OA are far less severe than those observed in rheumatoid arthritis (RA) which represents a primary inflammatory arthritis (Fingleton et al., 2015). Secondly, changes associated with inflammation are probably a more common phenomenon in asymptomatic adults than previously supposed and the natural history of synovial changes and any causal link with incident OA still needs further clarification.

1.4.5. Pain mechanisms

Pain experience in people with OA is highly heterogeneous between individuals varying from spontaneous mechanically induced pain to constant “dull”, “aching” pain. Two main underlying mechanisms in pain physiology adaptation that may help account for this variation are peripheral and central sensitisation. A joint specific pain at the early stage of OA typically is attributed to peripheral sensitisation and is characterised as spontaneous mechanically induced pain relieved by rest. A constant “dull”, “aching” more diffuse knee pain is usually attributed to central sensitisation.

Sensitisation is an increase in response to repeated stimulation. Peripheral sensitisation normally reflects the increased neuronal activity from the periphery caused by a tissue alteration or potentially tissue-damaging factors, neuropeptides and inflammatory mediators (Schaible, 2012, Dimitroulas et al., 2014). However, the amount of pain perceived cannot be fully explained by the amount of structural changes mainly because of a modulatory system within the nervous system which regulates and modulates the intensity of pain experienced. Plasticity changes in the central nervous system at the spinal or cortical level (central sensitisation) may arise as a result of the chronic increased peripheral sensitisation, or altered psychological state (anxiety, depression, multiregional pain or other conditions). Clinically, central sensitisation may produce allodynia (i.e., pain experience from a normally non-painful stimulus) and hyperalgesia (increased pain sensation at lower levels of pain stimulation at extended and remote

areas from the affected joint) (Luch et al., 2014, Kittelson et al., 2014, Fingleton et al., 2015, Neogi, 2013, Hochman et al., 2013). Amplification of painful and non-painful signals within the nervous system and reduction in descending inhibitory pathways forms the basis of sensitisation in chronic pain (Brooks and Tracey, 2005).

Several methods have been developed to measure central sensitisation in people with OA such as quantitative sensory testing (QST) and the PainDETECT questionnaire (PDQ) (Fingleton et al., 2015). For example, possible neuropathic-like pain defined using PDQ has been reported in 15% to 33% of people with knee OA (Valdes et al., 2014, Ohtori et al., 2012, Hochman et al., 2011). Interestingly, the central sensitisation associated with severity of symptoms is possibly independent of structural disease severity (Fingleton et al., 2015), which may help explain the discrepancies between severity of knee pain and radiographic changes (Finan et al., 2013).

1.4.6. Osteoarthritis subsets

OA shows wide variability between individuals in terms of age of onset, joint distribution, risk factor profile, symptoms, severity, structural features, and structural and symptom progression. Since the time that OA (“hypertrophic arthritis”) was first separated from RA (“atrophic arthritis”), discrete conditions such as diffuse idiopathic skeletal hyperostosis (DISH), ochronosis (due to alkaptonuria) and Kashin Beck disease (endemic environmentally induced chondropathy) have been removed from under the umbrella term of OA, and many attempts have been made subsequently to delineate different subgroups within the OA population (Dieppe and Lohmander, 2005). The terms “subgroups”, “subsets” and “phenotypes” are often used to present the variability of a disease. Irrespective of the differences between these terms, the purpose of using them is the same - to delineate groups that each share the same mix of certain characteristics. In this section, some of the proposed subsets of OA, including but not limited to knee OA, are summarised.

1.4.6.1. Phenotypes according to single facets

Primary versus secondary OA. Primary OA is defined as sporadic development of OA in the absence of any main identifiable cause and is assumed to result from complex interaction of multiple systemic and local vulnerability risk factors. Conversely, secondary OA is defined as OA that appears to result predominantly from a single recognised attributable risk factor (e.g. severe trauma, congenital or developmental disease, metabolic or endocrine abnormalities and other uncommon conditions)

(Altman et al., 1986). While primary OA is characterized by female predominance, positive family history of OA, and usually symmetrical polyarticular involvement of hand joints in the disease process (Vignon, 2000), “secondary” OA is usually described as more prevalent in men, often developing at a young age (<55 years old), and presenting mainly as a mono- or asymmetrical oligoarthritis because of the dominance of trauma as the cause (Cushnaghan and Dieppe, 1991, Brown et al., 2006).

However, recent studies have questioned the validity of this distinction. For example, the GARP (Genetics, Arthrosis and Progression) sibling study showed that people with obesity or meniscectomy were more likely to have a positive family history of OA in the hands, knees or hips in first-degree relatives (odds ratios (OR) 2.1, 95% CI 1.3 to 3.3, and OR 6.2, 95%CI 3.0 to 12.7, respectively) (Riyazi et al., 2008). Furthermore, people with radiographic changes of hand OA in middle age showed more frequent and more severe post-meniscectomy knee OA than those without hand OA (Doherty et al., 1983, Englund et al., 2004). Among individuals undergoing TKR those with post-traumatic OA had a slightly higher genetic contribution than those with non-traumatic OA (Valdes et al., 2013). Rather than two discrete entities of “primary” and “secondary” OA, these observations strongly support an interaction between generalised constitutional susceptibility and local adverse biomechanical factors in terms of causation, with their balance in a continuum (Brandt et al., 2009, Driban et al., 2010).

Single joint versus multiple joint OA. The number and distribution of joints affected by OA is commonly used to separate OA into different phenotypes (Zhang et al., 2005, Zhang et al., 2009, Zhang et al., 2010a, Felson, 2010, McAlindon et al., 2014). About 25% of people with OA have both hand and large joint OA and this has been counted as one of the OA phenotype (Nelson et al., 2014b). Individuals with nodal hand OA have higher risk of knee OA both for the development (Silverwood et al., 2015) and progression (Bastick et al., 2015, Valdes et al., 2010). This phenotype is mainly seen in middle aged women, often clustered within a family with a heritability of 42% (Felson et al., 1998). However, it is difficult to draw a clear distinction between generalised and non-generalised OA apart from multiple joint involvement. In addition, identification of a single joint involvement at one time-point doesn't mean no OA or subsequent risk of OA for other joints. This begs the issue of holistic examination and risk assessment to better understand current disease state and potential risk of developing multiple joint OA in order to optimise prevention and treatment.

Hypertrophic versus atrophic OA. Based on a relative dominance of bone formation or bone attrition, an early phenotypic separation for knee and hip OA was into “hypertrophic” and “atrophic” forms. The “hypertrophic” phenotype is characterized by large osteophytes, little JSN and extensive subchondral bone sclerosis whereas the “atrophic” phenotype presents with few osteophytes, severe JSN, destruction and loss of volume of subchondral bone (Conrozier et al., 2007, Roemer et al., 2012). There is reasonable evidence that “atrophic” hip OA is a risk

factor for more rapid disease progression (Lieveuse et al., 2002, Cheung et al., 2010) thus lending support to the clinical application and prognostic value of this classification at the hip. However, with respect to the knee both “atrophic” and “hypertrophic” phenotypes were very uncommon in the Framingham Knee OA Study (1.3% and 0.2% respectively) and both associated with more severe intra-articular structural damage than reference controls (Roemer et al., 2012). Therefore, the prognostic value and clinical usefulness of this classification at the knee remains unclear.

Biomechanical versus inflammation. Erosive hand OA (EOA) was reported first more than 40 years ago (Peter et al., 1966, Ehrlich, 1972a, Ehrlich, 1972b). It is characterised by more inflammation (Vlychou et al., 2009, Punzi et al., 2010, Zhang et al., 2009), a combination of bony proliferation and central/marginal subchondral erosions of articular surface, and overlapping histology with rheumatoid arthritis (Peter et al., 1966, Ehrlich, 1972a, Ehrlich, 1972b). It does appear distinct from nodal or non-nodal hand OA with more abrupt and severe clinical presentation, more rapid progression, interphalangeal instability, occasional spontaneous interphalangeal joint fusion, lack of association with OA elsewhere and worse outcome in comparison with non-erosive hand OA (Punzi et al., 2010). EOA is therefore considered as a typical inflammatory phenotype of OA. However, recent studies report that some EOA radiographic changes are not uncommon in people with hand OA (Marshall et al., 2015). Therefore whether EOA is part of the spectrum of hand OA or a discrete disease entity remains unclear.

Aside from EOA, whether there is an important inflammatory component to OA of knees and other joints, that may even drive the condition, is debated increasingly (Felson, 2013, Berenbaum, 2013). Although biomechanics and inflammation both play a role in OA development and progression it remains unclear as to which primarily drives OA initiation and progression.

Pain. OA is not only a joint disease, but a chronic painful condition with both peripheral joint damage and altered central pain processing (Dieppe and Lohmander, 2005). The central sensitisation plays a significant role in symptom severity in people with hand, hip and knee OA (Lluch et al., 2014). Moreover, pre-operative WSP sensitisation may be associated with increased risk of chronic pain after total knee and hip replacement (Wylde et al., 2013, Wylde et al., 2015, Aranda-Villalobos et al., 2013). Therefore, it has been suggested that people with knee OA whose pain is dominated by sensitisation may represent a distinct phenotype.

Metabolic syndrome. Multimorbidity is common in older adults (Doos et al., 2014) and many conditions share the same risk factors with OA. For example, age is a risk factor for OA, gout and calcium pyrophosphate deposition. Obesity is a risk factor for OA, cardiovascular diseases and diabetes (Felson et al., 1989). Several studies have found a significant link between metabolic disorders and OA, which has led to delineation of a phenotype associated with metabolic changes (Sellam and Berenbaum, 2013, Wang et al., 2015, Bijlsma et al., 2011, Herrero-Beaumont et al., 2009).

Metabolic syndrome and its components such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance have been associated with incidence and progression of OA and vice versa (Yoshimura et al., 2012, Schett et al., 2013, Louati et al., 2015). People with diabetes mellitus have greater risk of OA (OR 1.5, 95% CI 1.1 to 2.0), and people with OA have greater risk of diabetes mellitus (OR 1.4, 95% CI 1.2 to 1.6) (Louati et al., 2015). These findings indicate that systemic factors associated with obesity and metabolic disorders in addition to pathomechanical mechanisms play an important role in OA, though the precise mechanisms are not understood.

Both urate and calcium crystals may play a role in development of secondary crystal-induced synovitis and “flares” of OA. Urate crystals may directly damage joint tissue, and cause local inflammation and increase systemic levels of interleukin-18 (IL-18) and IL-1 β (Nowatzky et al., 2010, Denoble et al., 2011). There is evidence that hyperuricemia is associated with a higher risk of generalized OA (Acheson and Collart, 1975, Sun et al., 2000), and OA in turn increases risk of incident gout (adjusted OR (aOR) 1.3, 95% CI 1.2 to 1.3) (Kuo et al., 2016). A significant association between the site of acute attacks of gout and the presence of OA (aOR 7.9, 95% CI 6.3 to 10.1) suggests that OA changes can be a risk factor for localisation of urate crystal deposition (Roddy et al., 2007).

A potential role for calcium crystals in inducing synovial inflammation in OA joints (Rosenthal, 2011, Ramonda et al., 2014) and in having biomechanical effects on the cartilage in which they form has led to the

hypothesis that chondrocalcinosis (CC) may represent a subset of severe OA and play a role in disease progression (Ledingham et al., 1995). However, evidence for an association between CC and progression of the disease has yet to be established (Viriyavejkul et al., 2007, Neogi et al., 2006, Cheung et al., 2010, Doherty et al., 1996).

1.4.6.2. Phenotypes according to multiple facets

Over the last decade there have been several attempts to phenotype OA into different subsets according to several facets of the disease. Knoop (2011) proposed five clinical phenotypes based on a cluster analysis of four clinically relevant variables: severity of radiographic OA, lower extremity muscle strength, body mass index, and depression. These five phenotypes are “minimal joint disease”, “strong muscle”, “non-obese and weak muscle”, “obese and weak muscle” and “depressive” phenotypes. They also found that the outcomes of these five OA phenotypes are different in terms of knee pain and activity limitation. The results were replicated later in the Amsterdam Osteoarthritis (AMS-OA) cohort (Knoop et al., 2014, van der Esch et al., 2015).

There are several other proposals, all based on clinical expertise. Bijlsma et al. (2011) suggested five phenotypes: “post-traumatic”, “metabolic”, “pain”, “ageing” and “genetic”. Herrero-Beaumont et al. (2009) proposed three possible phenotypes: “genetically determined”, “oestrogen hormone dependent” and “ageing related” phenotypes. Karsdal et al. (2014) suggested a possible division of individuals with OA into at least three different phenotypes based on the most actively involved joint

tissue (bone, cartilage or inflamed synovium) or the tissue with predominant manifestations - “traumatic,” “generalised” and “episodic subacute and acute inflammatory OA”. Table 1-3 summarises the attempts to phenotype OA according to multi-facets of the disease. While the majority of studies have used pain, muscle strength, obesity and trauma to phenotype OA, a few used radiographs, number of joints affected and central sensitisation. This suggests some important facets that may be used for future classification. However, the key questions are whether these facets are all that we need to consider for phenotyping OA and whether we can truly separate patients into several subgroups according to these facets. For example, the “minimal joint disease” and “depressive” phenotypes proposed by Knoop et al. (2011) might overlap as might the “genetically determined” and “oestrogen hormone dependent” phenotypes proposed by Herrero-Beaumont et al. (2009). In practice it is very difficult to dichotomise them into discrete subgroups. Furthermore, none of these phenotypes have been validated in relation to OA treatments (Felson, 2010).

Table 1-3. Proposed clinical phenotypes of OA

	Pain	Muscle weakness	Overweight/ obese	Multiple joints	Central sensitisation	Inflammation	X-rays, BML	Trauma	Family history	Comorbidities (metabolic syndrome)
Herrero-Beaumont et al. (2009)		+							+	+
Knoop et al. (2011)	+	+	+		+		+			
Bijlsma et al. (2011)	+		+					+	+	+
Karsdal et al. (2014)				+		+		+		
Steultjens et al. (2014)	+	+	+			+		+		

Note: BML – bone marrow lesions.

1.4.7. Osteoarthritis as a common complex disorder

Many attempts have been made to divide people with OA into different subsets according to shared commonalities. However, there is often overlap between the proposed subsets between individuals, or within individuals at different time points. Although dividing the heterogeneous OA population into more homogeneous subsets seems rational and important, the heterogeneity of OA does not necessarily mean that discrete phenotypes exist. OA is a common complex disorder and variation in clinical presentations and outcomes can be explained by variable complex interaction between multiple and varying risk factors exposed to different individuals at different time points of the disease course (Doherty, 2001, Brandt et al., 2003, Weeks and Lathrop, 1995). Indeed, the best fitted prediction models for OA contain a combination of genetic and environmental factors, and additive individual characteristics (Manek et al., 2003, Zhang et al., 2011a, Takahashi et al., 2010, Kerkhof et al., 2014, Andriacchi et al., 2014).

For example, although age is a risk factor of OA this may not be due to age itself but because age is a factor that brings together cumulative exposures and multiple local vulnerabilities, hence an increasing susceptibility of a joint to the disease over time. Other risk factors such as trauma or obesity may have different effects in different age groups (Roos et al., 1995, Felson, 2013). Acute trauma is often seen in younger active people leading to the majority of “post-traumatic OA”. Chronic repetitive microtrauma, however, is more common in older people with

reduced muscle strength, reduced proprioception, and co-ordination, and increased weight. Genetic predisposition may not alone trigger the disease but speed up the development of the disease. It itself is heterogenous and may be the origin of a malshaped or malaligned joint, or inefficient cartilage repair which in combination with other factors increase the risk of the disease (Felson, 2004b).

The concept of common complex disorder is also in line with our current understanding of OA as the failure of the inherent repair process of synovial joints that may be triggered by a variety of joint insults, and where the balance between the different types and severity of joint insults and the repair potential of the individual joint tissues confer the heterogeneity of clinical presentations and outcomes (Figure 1-3) (Brandt et al., 2003). The concept of a common complex disorder helps to better explain the findings of synovial hypertrophy and inflammation – as an integral part of attempted repair rather than the initiating and driving cause of the arthropathy. Furthermore, several subsets can be found in the same individual or one subset can later evolve to another (Castaneda et al., 2014, Karsdal et al., 2014). This suggests that OA is not a static disease, but a dynamic pathological process. This partially explains the failure of attempts to separate the entire population with OA into several clear subgroups.

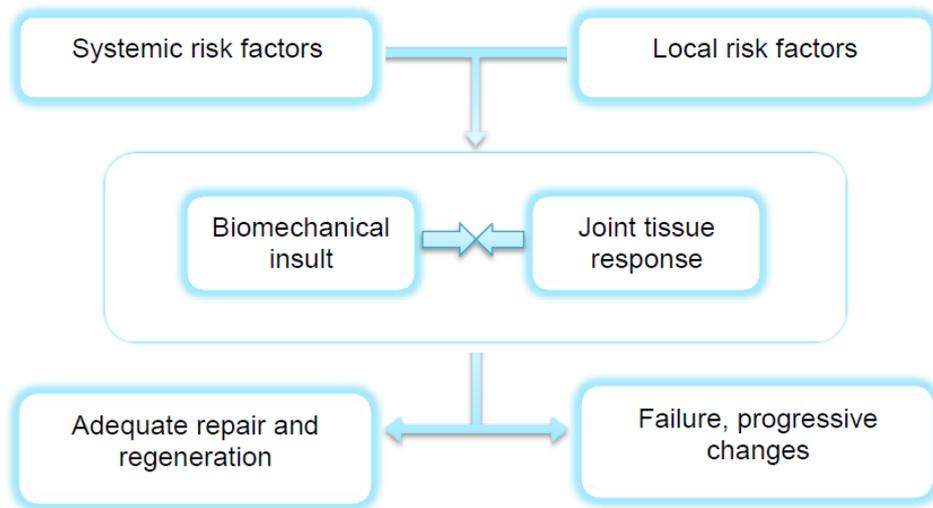


Figure 1-3. Schematic representation of relations between risk factors, pathology and outcomes.

A conceptual model of OA pathology assumes that a number of local and systemic risk factors causes uneven distribution of loading and damage. In response to this a set of regenerative and reparative processes occur in all tissues of the joint. The outcome depends on the balance between biomechanical insult and tissue response.

1.5. Imaging

Currently, the role of imaging in routine clinical practice for diagnostic purposes is limited. Individuals over 40 years with the typical presentation of OA do not require imaging assessment to help confirm the diagnosis of knee OA (Sakellariou et al., 2017). However, evaluation of structural features of OA including bone and soft-tissue abnormalities is essential for the understanding of the natural history of this condition and how multiple pathologies contribute to OA pain. For example, some structural changes might be detected by imaging before the presence of symptoms and allow an early treatment, whereas other structural changes might help to identify people who are more likely to have rapid progression or may respond better to certain treatments (Kraus et al., 2011).

1.5.1. Radiography

Conventional radiography has remained a gold standard in OA diagnosis and assessment of structural progression for more than 50 years (Kellgren and Lawrence, 1957). The radiographic assessment of knee OA generally includes the tibiofemoral and patellofemoral compartments. Two main measures can be seen on radiographs – formation of osteophytes at the joint margins or in ligamentous attachments and reduction in joint space width (JSW), often associated with sclerosis of adjacent subchondral bone.

Various methods have been developed to assess and grade structural severity of OA. The Kellgren and Lawrence (K&L) system is the most

commonly used semi-quantitative global scoring system. However, it has been criticised because it is ordinal not interval, is largely based on osteophyte score and might not define incident disease clearly or might not be sensitive to change, and also because of the lack of consensus regarding the descriptions and interpretations of the grades (Culvenor et al., 2015, Felson et al., 2011, Schiphof et al., 2011).

In order to further unify and standardise radiographic assessment and increase intra-reader and inter-reader reliability several atlases and grading methods have been developed. For example, the OARSI (OA Research Society International) photographic atlas (Altman et al., 1995, Altman and Gold, 2007), Ahlbäck score (1968), the Nottingham logically derived Line Drawing Atlas (NLDA) (Nagaosa et al., 2000, Wilkinson et al., 2005) and the Atlas of Knee Images Digital Analysis (Marijnissen et al., 2008).

Global scales such as K&L system provide specific verbal descriptions for each grade (Sheehy and Cooke, 2015). Composite scales such as the OARSI atlas or the NLDA measure individual features of OA which then can be combined as a total score (Sheehy and Cooke, 2015). These individual OA features (grades of osteophytes, JSN and other features) can be also used alone without total summated score. Advantages of the NLDA is that it provides an interval scale for JSN and osteophyte size, and separate JSN images for men and women to account for the normally thicker cartilage width in men (this is ignored in all other grading systems). However, radiography as a method has limitations for

assessing OA structural changes because of the two-dimensional image, only indirect assessment of cartilage thickness, insensitivity for detecting bone changes, and inability to assess menisci, synovium, capsule or peri-articular structures (Iagnocco, 2010, Hensor et al., 2014).

1.5.2. Magnetic resonance imaging

MRI is now the most sensitive modality for imaging the entire spectrum of OA-related cartilaginous and non-cartilaginous abnormalities in the knee in three dimensions, most of which are undetected by plain radiographs. Thus, MRI is able to detect subchondral bone loss (attrition), bone marrow lesions, cartilage and meniscal lesions, effusion, synovitis, ligaments and tendons (Hunter et al., 2011b, Alizai et al., 2015). Some MRI findings such as osteophytes, cartilage volume, bone marrow lesions and meniscal tears have been studied widely and were included in the standard definitions of OA on MRI accepted by OARSI (Hunter et al., 2011a). Moreover, MRI assessment of cartilage morphology was recommended as an optimal outcome measure for longitudinal trials of OA structure modification (Conaghan et al., 2011).

With respect to the synovial changes detected by MRI, the techniques and methods of better visualisation are still evolving. For example, contrast-enhanced MRI (CE-MRI) offers a more accurate evaluation of synovitis than plain MRI, because without gadolinium contrast injection it is not possible to distinguish synovial fluid (i.e. joint effusion) from the synovium (Hayashi et al., 2014, Gait et al., 2016). On non-contrast MRI

the hyper-intensity within Hoffa's fat pad or the composite effusion-synovitis score are the surrogate markers of synovitis, which were reported to have an association with histological signs of mild synovitis in a study by Fernandez-Madrid et al. (1995). However, a more recent comparative study conducted by Loeuille et al. (2009) showed that only synovitis detected by CE-MRI correlates with microscopically-detected synovitis. The moderate association between synovitis on CE-MRI with microscopic and macroscopic features of synovial tissue inflammation was also confirmed in a study by de Lange-Brokaar et al. (2014).

MRI has contributed greatly to the understanding of the OA disease process at the knee. Although infrapatellar synovitis and knee effusion detected by CE-MRI are strongly associated with radiographic severity (OR 9.05, 95% CI 1.94 to 42.3, and OR 5.75, 95%CI 1.23 to 26.8, respectively) (Krasnokutsky et al., 2011), early knee pathology may precede incident ROA or predict progression of established OA. Hoffa-synovitis, effusion-synovitis and medial meniscal damage were associated with a higher risk of incident ROA in the OA Initiative (OAI) Cohort (ORs 1.76, 95%CI 1.18 to 2.64, and 1.81, 95%CI 1.18 to 2.78, and 1.83 95%CI 1.17 to 2.89, respectively) (Roemer et al., 2015). People at high risk of knee OA with effusion-synovitis detected by MRI were more likely to have cartilage loss after a 30-month follow-up in the Multicenter Osteoarthritis Study (MOST) cohort (n=514, aOR 2.7, 95% CI 1.4 to 5.1) (Roemer et al., 2011). The increased contact stress on MRI predicted incident symptomatic tibio-femoral OA 15 months later in the MOST Cohort (Segal et al., 2009). Although conflicting evidence exists for

relationships between MRI findings (cartilage volume loss) and radiographic progression (defined by JSN), the majority of studies report a positive association (Hunter et al., 2011b).

Secondly, some MRI findings such as bone marrow lesions (BML) and effusion-synovitis have a moderate association with knee pain. A systematic review by Yusuf et al. (2011) demonstrated that ORs of having pain range from 2.0 (no CI was given) to 5.0 (95% CI 2.4 to 10.5) in people with BML and between 3.2 (95% CI 1.04 to 5.3) and 10.0 (99% CI 1.1 to 149) in people with effusion/synovitis. Moreover, the relationships between MRI-findings and knee pain demonstrated a dose-response pattern. Changes in the BML score and synovitis score were also associated with changes in the frequency of knee pain ($p=0.006$ and $p=0.045$ for trend), whereas a decrease in the size of BML was associated with a reduction of knee pain ($p=0.007$ for trend) (Zhang et al., 2011b). The severity of synovitis on CE-MRI was also associated with an increased risk of pain (aORs for moderate/severe/extreme pain vs no pain for some synovitis 2.0, 95%CI 1.1 to 3.6, and for a lot/extensive synovitis 9.2, 95%CI 3.2 to 26.3) (Baker et al., 2010).

Although MRI is an effective diagnostic tool for identifying multiple tissue pathology, it does not explain entirely the link between structural changes and symptoms of knee OA (Baert et al., 2014). Moreover, early MRI findings can often be found in asymptomatic individuals and therefore lead to over diagnosis or misdiagnosis (Guermazi et al., 2012). For example, a recent population-based study ($n=977$) demonstrated that

effusion-synovitis (Whole-Organ Magnetic Resonance Imaging Score (WORMS) grade ≥ 2) is common in older adults (67%) and the association between effusion-synovitis at the suprapatellar pouch (42.9%) and changes in cartilage volume and BML during 2 year follow-up becomes non-significant after adjustment for cartilage defects (Wang et al., 2016a). This suggests that the natural history of synovial changes detected by MRI and a causal link with incident OA still requires further study. In addition MRI is an expensive and time-consuming method to use in routine clinical practice and therefore it is often considered unnecessary for the majority of people with knee pain.

1.5.3. Ultrasound

US imaging is another imaging modality that has become popular with rheumatologists because it is non-invasive, has no radiation burden, is relatively inexpensive, involves a short examination time, and has good patient acceptability (Iagnocco, 2010). Over the last two decades a number of technical advances have improved US imaging of joints and soft tissues increasing its utility for assessment of musculoskeletal conditions (Bureau and Ziegler, 2016). According to one survey, 93% of the rheumatologists in the United Kingdom (UK) use musculoskeletal US for patient management, and 33% of them perform US themselves (Cunnington et al., 2007). A study undertaken by Micu et al. (2013) demonstrated that musculoskeletal US is a useful bedside diagnostic tool in rheumatological practice, allowing a more detailed and objective initial clinical diagnosis and definitive therapeutic decisions at the first visit, thus

helping to optimise health resources. For example, although a large and medium sized effusion can be detected visually or by performing simple clinical tests such as the patellar tap test, fluid displacement (bulge, wipe or stroke test) or “balloon sign” test for fluctuance (Maricar et al., 2016), US is more sensitive than clinical examination (Karim et al., 2004, Ulasli et al., 2014). US correlates well with histological findings (Walther et al., 2001, Labanauskaite and Sarauskas, 2003) and is equivalent to MRI in visualising effusion (Tarhan and Unlu, 2003, Aleo et al., 2014).

1.5.3.1. Synovial changes detected by ultrasound

High-resolution grey-scale or B-mode US can depict a range of radiographically invisible abnormalities in the hyaline cartilage, synovial membrane, menisci, tendons, ligaments, joint capsule and bursae in and around the knee joint (Martinoli and Bianchi, 2007). In people with OA, synovial pathology is the single most studied imaging feature (Keen et al., 2009, Iagnocco, 2010). A number of studies have observed significant associations between knee pain and synovial changes detected on US such as effusion (D'Agostino et al., 2005, Ulasli et al., 2014, Hall et al., 2014, Malas et al., 2014, de Miguel Mendieta et al., 2006) and synovial hypertrophy (D'Agostino et al., 2005, Hall et al., 2014). Synovial changes detected on US in people with knee pain and knee OA have also been shown to predict disease outcome. Effusion was associated with increased risk of subsequent joint replacement in one EULAR study (hazard ratio (HR) 2.63, 95%CI 1.70 to 4.06) (Conaghan et al., 2010). The association was stronger for those with knee pain at baseline (HR 1.81, 95% CI 1.15 to 2.83) and longer disease duration (HR 1.63, 95%

CI 1.08 to 2.47), but not as strong as the association between joint replacement and K&L \geq 3 (HR 4.08, 95% CI 2.34 to 7.12) (Conaghan et al., 2010).

Since effusion and synovial hypertrophy show a fluctuating pattern in prospective US studies (Beyers et al., 2014), it was supposed that these features may offer the potential to detect or even predict treatment response. Some studies reported trends that synovial pathology reduces with time after local therapy, however, the systematic review of Keen et al. (2009) reported limited evidence for the ability of US to detect changes over time (i.e. discriminant validity). Recently, based on a small study (n=35) Keen et al. (2015) demonstrated changes in effusion, synovial thickness and Power Doppler signal (PDS) one week after intra-articular steroid injection, though changes were not significant after 4 weeks. Therefore the role of synovial changes detected on US in predicting response to intra-articular injections is still unclear (Maricar et al., 2013).

Doppler is another US modality used to detect increased perfusion in synovium and peri-articular tissues (Joshua et al., 2006). There are two types of Doppler assessment such as Colour Doppler and Power Doppler which evaluate and represent different aspects of blood flow (Torp-Pedersen et al., 2015). Colour Doppler measures the direction (up or down) and the mean velocity of moving erythrocytes, whereas Power Doppler measures the shift in wavelength (frequency) of sound caused by the moving erythrocytes regardless of the direction and velocity of the flow. This advantage makes Power Doppler assessment very sensitive

to slower flow rates within small vessels (Martinoli et al., 1998, Torp-Pedersen et al., 2015). For clarity we will use the term “Doppler signal” (DS) if it refers to both Colour and Power Doppler or if the type of DS was not specified in the original source.

A positive DS is associated with clinical signs of inflammation such as soft tissue swelling, tenderness, and increased warmth, and also with histology and laboratory markers of inflammation (e.g. serum CRP) in people with inflammatory arthritis such as RA, spondylo-arthropathy and juvenile chronic arthritis (Joshua et al., 2006), as well as in normal joints with increased tissue hyperaemia following joint overuse (Koski, 2012). Comparative studies show that although DS in synovium in individuals with knee OA is not as common and widespread as in people with RA, it correlates well with histological findings in both groups (Walther et al., 2001, Labanauskaite and Sarauskas, 2003).

1.5.3.2. Normal US anatomy and standard definitions

US examination of synovial changes includes anterior, medial and lateral aspects of the knee. The suprapatellar recess is the widest recess of the knee joint located proximal to the patella between the quadriceps tendon and femur. It consists of midline, medial and lateral parts (Bianchi and Martinoli, 2007). On longitudinal images the suprapatellar recess can be seen as a thin hypoechoic space (collapsed anterior and posterior synovial membrane) between the triangular suprapatellar fat pad and the large pre-femoral fat pad on two sides (Figure 1-4A). The medial aspect of the knee joint is defined as the area medial to the patella running

inferiorly past the medial joint line to the infero-medial aspect of the joint capsule. This area consists of the medial collateral ligament, medial femoro-tibial space and medial meniscus. The medial collateral ligament is formed by two distinct layers (superficial and deep) with a synovial bursa (medial collateral ligament bursa) between them. In normal states, it cannot be seen on US (Bianchi and Martinoli, 2007). The lateral aspect of the knee is defined as the area lateral to the patella running inferiorly past the lateral joint line to the inferolateral aspect of the joint capsule. This area is formed by the distal aspect of the iliotibial band, the external femoro-tibial joint space with the lateral meniscus, the lateral collateral ligament, and the superior tibio-fibular joint.

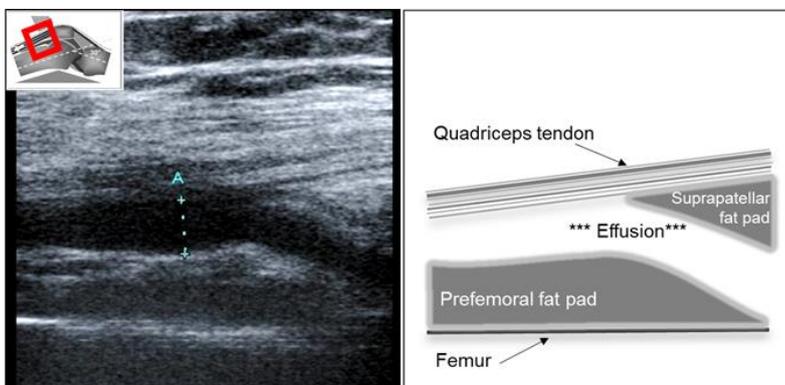
Examination routinely starts from the suprapatellar recess, followed by the medial and then lateral aspects of the knee (Bianchi and Martinoli, 2007). Among three compartments of the suprapatellar recess, amount of effusion is greater in lateral recess compared to midline and medial recesses (Hirsch et al., 2012). However, a study by Karim et al. (2004) showed that synovial hypertrophy detected in three areas of the knee including suprapatellar recess, medial and lateral aspects, has an accuracy of 97% compared with synovitis detected using arthroscopy (gold standard). There was a non-significant difference in sensitivity between the three areas (Karim et al., 2004).

Standard definitions for effusion and synovial hypertrophy detected on US were recommended by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Special Interest Group (Wakefield et

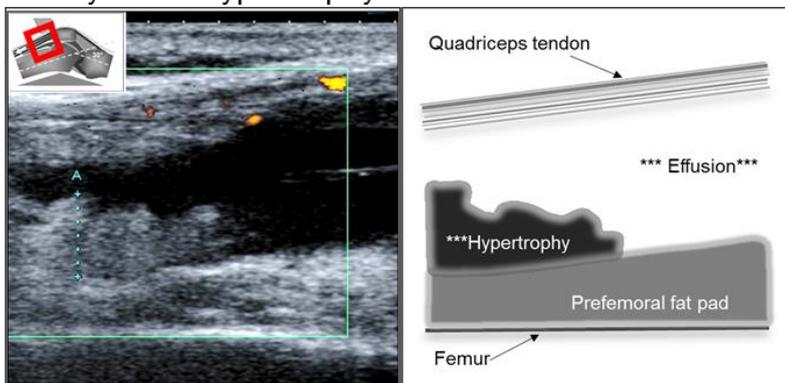
al., 2005). **Synovial effusion** was described as an “abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hypoechoic) intra-articular material that is displaceable and compressible, but does not exhibit DS”. **Synovial hypertrophy** was defined as “abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular tissue that is non-displaceable and poorly compressible and which may exhibit DS” (Wakefield et al., 2005).

The integrated use of Power Doppler and grey-scale imaging allows detection of increased blood flow in the synovium, particularly in areas of synovial hypertrophy (Figure 1-4). PDS is usually recorded dichotomously as absent or present, or scored on a semi-quantitative scale (0 = absence of flow; 1 = mild: up to 3 single spots signals or up to 2 confluent spots or 1 confluent spot + up to 2 single spots; 2 = moderate: vessel signals in <50% of the area of the synovium (but more than grade 1); 3 = marked: vessel signals in >50% of the area of the synovium) (Iagnocco et al., 2010).

A. Effusion



B. Synovial hypertrophy



C. Power Doppler signal

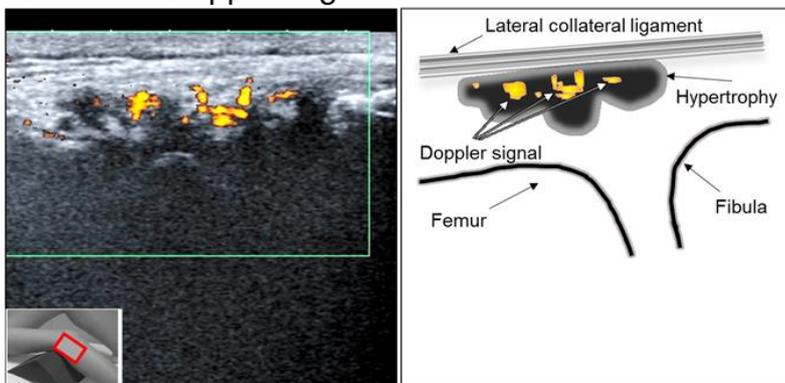


Figure 1-4. Grey-scale US image of an effusion and synovial hypertrophy in the supra-patellar pouch, and Power Doppler signal in the lateral tibio-femoral space of the knee.

Note: On the left the real US images with detected synovial pathology (taken from study participant); with images of the knee area and position (adapted from (Bianchi and Martinoli, 2007), permission granted); on the right are schematic drawings synovial pathology in relation to other joint structures.

Despite the common use of US in assessment of the knee joint, information regarding normal values for effusion and hypertrophy in the general population is limited (Sarmanova et al., 2016). For example, the only study to provide reference values for effusion was based on a group of healthy volunteers aged from 20 to 60 years old (n=102) (Schmidt et al., 2004) which is a low age range for OA, and no studies have examined synovial hypertrophy or prevalence of PDS. Also, whether synovial changes detected on US differ according to age, gender or laterality remains unknown. A few studies have attempted to identify an optimal threshold or scoring system for synovial changes detected on US associated with knee OA. For example, a EULAR-ESCISIT multi-centre study involving 600 individuals with knee OA tested different cut-offs of synovial hypertrophy ($\geq 2\text{mm}$ or $\geq 4\text{mm}$) and effusion ($\geq 4\text{mm}$) against radiographic severity and knee joint effusion on clinical examination (Conaghan et al., 2005). The diagnostic accuracy of these cut-offs was low and it was recommended that a threshold of 4 mm be used for both features (D'Agostino et al., 2005).

Two European Multicentre Studies also found that thresholds varied depending upon knee positioning. While Terslev et al. (2012) (n=149) found the best predictive value had a threshold of 3.2 mm for knee effusion detected in the neutral position with quadriceps contraction, Mandl et al. (2012) showed that the best cut-off value for effusion at 30 degrees of flexion is 3.6 mm. However, these studies have only included people with knee OA or other rheumatic conditions and their findings have not been compared with the general population or healthy controls,

hence the thresholds between knee OA and the normal population remain to be established.

Furthermore, none of the existing recommendations for scoring synovial changes detected on US have considered age, gender or laterality. Interestingly, the EULAR-ESCISIT study in people with knee OA noted that women had fewer joint effusions than men (OR 0.62, no CI reported) (D'Agostino et al., 2005) but they still recommended the same threshold (4mm) for both men and women. The difference in joint anatomy, physiology, pain perception and risk of incidence and progression of OA between genders provides a clear physiological basis for examining whether there is a difference in synovial changes detected on US between men and women (Srikanth et al., 2005).

US is still a developing method in terms of improvement and standardisation of definitions and scoring techniques. Despite the increased interest in the role of US in people with knee pain/OA, the information regarding normal ranges for effusion and hypertrophy derived from the general population is limited (Schmidt et al., 2004). The value of the currently recommended threshold has never been validated in the general population or in healthy controls. Therefore, the normal ranges, the natural history of US-detected changes, their associations with knee pain and prognostic value still need further clarification (Iagnocco, 2010).

1.6. Management of knee osteoarthritis

Current management of knee OA includes non-pharmacologic, pharmacologic and surgical treatments. Overall there is agreement between rheumatology organisations such as ACR, EULAR, OARSI and others that non-pharmacologic modalities such as education, self-management, exercise, weight loss if overweight, walking aids and local thermal modalities if indicated should be considered for all patients with knee and hip OA (Nelson et al., 2014a). Recommended pharmacologic modalities for knee OA are acetaminophen/paracetamol as first-line oral analgesic treatment and non-steroidal anti-inflammatory drugs (NSAIDs) as a second-line systemic analgesic option. Topical agents (topical capsaicin and topical NSAIDs) are recommended as another first-line analgesic option by the National Institute for Health and Care Excellence (NICE) (Conaghan et al., 2008) and intra-articular corticosteroids are another universally recommended local pharmacological treatment, especially for more severe pain or exacerbations of pain that are resistant to other analgesic approaches (Nelson et al., 2014a). A joint replacement is recommended when needed, whereas arthroscopy with debridement is not (McAlindon et al., 2014). Since individuals with symptomatic OA present unique sets of clinical, structural and somatosensory characteristics, guidelines recommend an individualised approach for all patients with OA in order to enhance the effectiveness of treatment (Conaghan et al., 2008, McAlindon et al., 2014). The sequential approach to the management of OA is presented in Figure 1-5 (Dieppe and Lohmander, 2005).

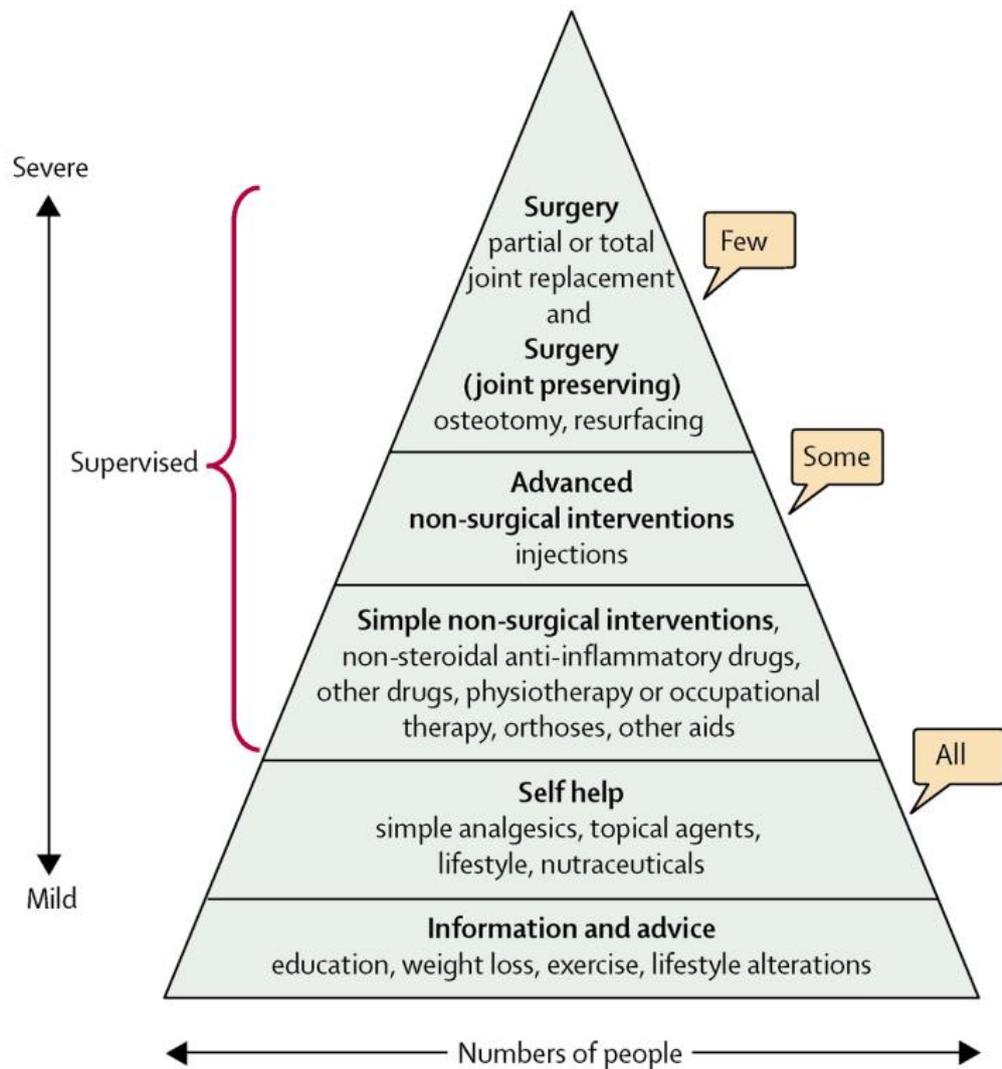


Figure 1-5. Principles of the management of osteoarthritis.

Suggested sequential, pyramidal approach to disease management (Dieppe and Lohmander (2005), permission granted).

Ideally, treatment of OA should optimise biomechanics and relieve pain, but also prevent joint failure by targeting at specific points of the pathogenic pathway potentially affecting different tissues, specifically bone, cartilage, ligaments and synovium (Birrell and Felson, 2009). However, at present management of OA remains mainly symptomatic since disease modifying effects of several proposed treatment methods has not been conclusively proven (Gallagher et al., 2015). Moreover, of the 51 treatment modalities developed for OA only a few (e.g., oral opioid and intra-articular steroid injection) reach the minimum clinical important difference (MCID) threshold over placebo (Zhang et al., 2010b, NICE, 2014). Many people with OA continue with symptoms and disability despite treatment and the number of people requiring total joint replacement (TJR) keeps increasing (Weinstein et al., 2013, Losina et al., 2012). In addition, recent evidence shows that 15% to 30% of people still experience pain after TJR (Wylde et al., 2011, Wylde et al., 2013). While we await the development of novel more effective treatments for OA, optimisation of existing treatments has become a major research interest (Karsdal et al., 2014, Bruyère et al., 2015).

1.7. Summary

Knee pain, the main symptom of knee OA, affects one in 4 people aged over 55 years, of whom 10% have mild-to moderate disability (Peat et al., 2001). The prevalence of knee pain and knee OA continues to rise because of increasing longevity and obesity, causing a significant socio-economic burden (Zhang, 2010, Puig-Junoy and Ruiz Zamora, 2015). The aetiology of knee pain is heterogeneous and its relationship with OA structural changes and function is unclear. It is well recognised that development and progression of knee pain/OA are influenced by a combination of risk factors relating both to systemic susceptibility, including altered central pain processing, and to local joint pathophysiology (Brandt et al., 2003, Phillips and Clauw, 2013, Doherty, 2001, Felson, 2004a). A complex interaction between different risk factors results in heterogeneity of clinical presentations and outcomes (Cohen and Lee, 2015).

Pathologically OA is characterised by involvement of all joint tissues, typically with focal cartilage loss, osteophyte formation, subchondral bone remodelling, and synovial and capsular thickening. At the knee level both biomechanical factors and inflammation play a role in OA development and progression but there are contrasting views as to the relative importance of each. The main controversy involves the origins of synovial inflammation and whether it is “secondary” to the other causes and intra-articular processes or may be “primarily” in terms of initiating and driving pain and structural OA (Berenbaum, 2013). Although synovial hyperplasia in knees affected by OA is focal and less marked than in

knees with RA it may still play an important role in disease pathogenesis (Hayashi et al., 2011, Attur et al., 2010). US is a commonly used imaging modality to detect soft-tissue changes at the knee joint (Iagnocco, 2010). Therefore, whether synovial changes detected by US could be a potential biomarker of inflammatory response and therapeutic target in OA is an important research question (Attur et al., 2010).

1.8. Rationale and study objectives

Recently, an important role for synovial pathology, specifically synovitis, in the initiation and progression of knee OA has been emphasised (Sokolove and Lepus, 2013, Berenbaum, 2013, Driban et al., 2010, Siebuhr et al., 2014). With the increasing focus on precision medicine, synovial pathology has been proposed as a potential target for therapeutic intervention or as a biomarker to define a group of people who require specific (e.g. anti-inflammatory) therapy (Mathiessen and Conaghan, 2017).

A number of predominantly hospital-based studies have been undertaken in knee OA to examine US detected abnormalities. However, the normal values, thresholds and frequencies of these features in the general population and in community-based people with knee pain or OA remain largely unknown. Therefore, it is of interest to systematically review studies of synovial effusion, synovial hypertrophy and positive DS in the general population and in people with knee pain or knee OA and, if possible, the prevalence and associations of such changes, before designing and conducting further studies. Moreover, it is important to know whether synovial changes detected on US associate with knee pain and predict changes in symptoms over time, especially in early disease where treatments such as surgery would be inappropriate (D'Agostino et al., 2014, Keen et al., 2011). Furthermore, previous studies have reported that radiographic structural changes, a strong risk factor for knee pain (Neogi et al., 2009, Wesseling et al., 2015), also positively associate with US-detected findings (Hall et al., 2014). Therefore, in order to explore the

relationships between knee pain and synovial changes it is important to account for radiographic structural OA. The effect of these risk factors may also differ in early and advanced OA (van Dijk et al., 2006, Jones et al., 2016), and the lack of studies in people recruited from the community (Jinks et al., 2008) also may influence the generalisability of previous results (Kraus et al., 2011).

The objectives of my PhD project include:

1. To systematically review the literature on synovial changes detected by ultrasound in people with knee pain/OA and/or in the general population in order to identify, critically appraise and summarise the findings of all relevant individual studies.
2. To establish the normal ranges for synovial thickness and effusion and determine an optimal cut-off associated with knee pain and ROA in community-derived men and women over 40 years old.
3. To examine whether community-derived people with early or established knee pain are more likely to have synovial changes detected on US, specifically effusion, synovial hypertrophy and PDS, compared to controls without knee pain and to explore whether synovial changes detected on US predict/associate with subsequent knee pain worsening.
4. To explore the role of peripheral risk factors, including synovial changes detected on US, and central risk factors that may influence pain experience in community-derived people with knee pain compared to pain-free controls, including the role of synovial changes detected on US in different types of knee pain.

2. METHODS

This chapter describes the resources and methods that are used in this thesis, including details of the source population, designs of all studies undertaken, definitions of outcome/exposure measures and confounding factors. Detailed protocols for the US and radiographic assessments are presented. This chapter also describes my training in musculoskeletal US and knee radiographic assessment undertaken prior to the study, including establishing intra and inter-observer reliability. The statistical analysis section describes the study sample size and power calculations and the specific methods used.

2.1. Systematic review and meta-analysis

2.1.1. Data sources and search strategy

Two systematic literature searches were performed in May 2015. Six electronic databases were used: Medline (1946–), EMBASE (1974–), Allied and Complementary Medicine (1985–), PubMed (1960–), Web of Science, and SCOPUS (1960–). Citations and abstracts retrieved from this search were downloaded to EndNote X6.0.1 (licensed to The University of Nottingham).

The first search included (a) OA of the knee, and (b) ultrasound. The search terms were “[ultrasound or sonography or ultrasonography or doppler or dopplerography or power-doppler] and [knee osteoarthritis or knee osteoarthrosis or gonarthrititis or gonarthrosis or knee pain or ((osteoarthritis or osteoarthrosis or osteophyte or joint space narrowing or degenerative joint disease(s)) and knee)]” (Appendix 1).

The second search was performed for studies that have explored prevalence of synovial changes in the general population irrespective of knee pain or knee OA using terms “[knee(s) and [ultrasound or sonography or ultrasonography or doppler or dopplerography or power-doppler] and [normal or healthy or general or population-based]” (Appendix 1).

2.1.2. Selection criteria

Observational studies were included if they examined US-detected synovial effusion, synovial hypertrophy or DS detected in people with knee pain/OA, in the general population or in normal/healthy controls. If studies were based on the same participants and same outcome measures, only one publication with the most detailed information was included in the review. There were no language restrictions.

Randomised controlled trials, studies in selected groups with synovial effusion or synovial hypertrophy, studies without clear definition of US-detected pathology (for example “synovitis” without description whether it is related to synovial hypertrophy or a combined measure of effusion and hypertrophy), or studies not reporting the prevalence estimate were excluded as they cannot provide an adequate estimate of prevalence. Although reviews and conference proceedings were not included their references were cross-checked.

2.1.3. Data extraction and outcome measures

For each included article information on authors, year of publication, study design (cross sectional, case control), population (hospital, community), sample size, age, gender, BMI, diagnostic criteria (e.g. ACR), radiographic score (e.g., K&L score), and US findings were systematically extracted using a specifically developed data extraction form and then transferred to a database.

The primary outcome measure was frequency/prevalence of US effusion, synovial hypertrophy and DS in people with knee pain/OA and in a control or general population derived directly or indirectly from information provided in each study. The secondary outcome measure was the association of US features with OA clinical features (pain, impaired function) and radiographic structural damage. Scores for pain intensity were standardised to a common 0 (no pain) to 100 (worse pain) scale.

2.1.4. Quality assessment

The Newcastle-Ottawa Scales (NOS) were used for observational studies e.g., case-control and cross-sectional studies (Wells et al.) as recommended by the Cochrane Non-Randomized Studies Methods Working Group (Reeves et al., 2011). Three main criteria were assessed: participant selection and representativeness, comparability of study groups, and assessment of outcome or exposure. The quality score is based on a "star" system (range 0 to 9 stars for case-control studies and from 0 to 10 for cross-sectional studies) with a higher score representing better methodologic quality. The percentage of the maximum score achieved was used to present the quality of each study.

2.1.5. Statistical analysis

To derive a pooled estimation of prevalence across different studies, the random effects meta-analysis was undertaken using the "METAPROP" package (with the Freeman–Tukey double arcsine transformation and

exact binominal CI for prevalence). Heterogeneity between studies was measured using the I^2 and Q test (Higgins et al., 2003, Higgins and Thompson, 2004, Harris et al., 2008). 95% CIs and a p value of 0.05 were used for a statistically significant inference. Publication bias was assessed using funnel plots and Egger's test (Steichen, 1998). If the number of studies included in the meta-analysis was too small (≤ 4) the Harbord test was applied to measure publication bias (Harbord et al., 2009). Statistical analysis was undertaken in Stata SE software V13.1 (StataCorp LP, College Station, TX, USA) (Nyaga et al., 2014, Chaimani et al., 2014).

2.2. Research ethics

The Knee Pain and Related Health in the Community (KPIC) study was approved by the Nottingham University Hospitals NHS Trust and the Nottingham Research Ethics Committee 1 (Ref 14/EM/0015) and registered on the clinicaltrials.gov portal (NCT02098070).

The nested cross-sectional study for US normal values in the general population was approved by the Nottingham Research Ethics Committee 1 (Ref 15/EM/0529) and by the Nottingham University Hospitals Research and Innovation Department (Ref 15RH015) (Appendix 2). Supporting documentation, study protocol, participant information sheets and consent forms are included in Appendix 3.

2.3. KPIC cohort study: description

The source population for all studies undertaken for this Ph.D was the KPIC cohort. The KPIC study was designed and conducted within Academic Rheumatology, University of Nottingham. This is an observational prospective study aimed to determine the prevalence and variation of self-reported knee pain characteristics in a community-derived sample of adults at baseline and then one year and 3 years later.

At baseline approximately 40,000 postal questionnaires concerning knee pain, other body pain, risk factors for OA, and general health were sent via their general practice surgery to people aged 40 years and over who were registered in general practices in Nottinghamshire. In total, 9,506 people returned completed questionnaires at baseline (response rate 23.8%). A second questionnaire was posted one year later to the 6716 participants who indicated willingness to receive a further questionnaire and who were alive. Responders to the Year 1 questionnaire (n=4738, response rate 70.6%) reported a higher frequency of knee pain and pain severity at baseline compared to the whole study population (n=9506) (Table 2-1).

At the stage of the baseline postal survey potential participants were excluded by their respective general practitioner if terminally ill, severely demented, or suffering from severe psychiatric illness, or any other condition or circumstance that makes them unsuitable to receive the questionnaire. In addition to this, at the stage of clinical assessment (for both cross-sectional and case-control study) exclusion criteria were:

knee arthroplasty; major prior knee/lower limb injury; or current pregnancy.

Table 2-1. Characteristics of the baseline and follow-up populations

	Baseline (N=9506)	Follow-up (N=4738)	P-value*
Age (years), mean (SD)	62.10 (10.56)	62.47 (10.14)	0.0007
Women, n (%)	5372 (56.51)	2741 (57.85)	0.0583
BMI, mean (SD)	27.31 (5.30)	27.26 (5.30)	0.3165
Prevalence of knee pain, (%)	4288 (45.10)	2396 (50.57)	<.0001
Prevalence of current knee pain, (%)	2681 (28.20)	1471 (31.05)	<.0001
Current knee pain severity (NRS 0-10), mean (SD)	1.97 (2.96)	2.15 (3.00)	<.0001

Note: * p-value for the difference between responders to follow-up questionnaire and the whole baseline population.

SD - standard deviation; BMI - body mass index; NRS – numerical rating scale (range 0-10).

A summary flowchart of recruitment for the nested cross-sectional and case-control studies from the original KPIC cohort is presented in Figure 2-1.

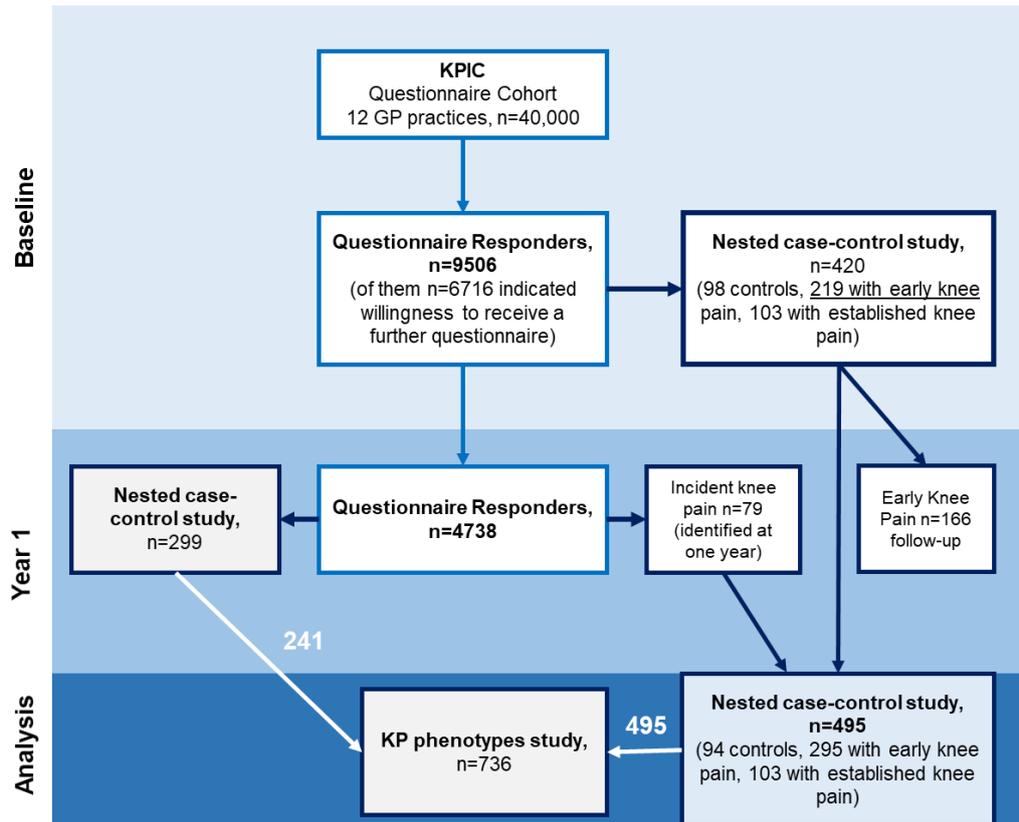


Figure 2-1. Recruitment of participants from the KPIC cohort.

2.4. Study designs and participants' selection

2.4.1. Nested cross-sectional study for ultrasound normal values in the general population

Participants for this nested cross-sectional study were selected from the KPIC cohort randomly regardless of their knee pain status. Men and women were separated and a simple random sample was taken from each group. A random number was assigned to each participant as key, then all participants were sorted in ascending order using the key and the first 500 numbers were selected.

For convenience, participants for this study were selected from the general practices closest to the City Hospital. To ensure that this set is representative of the whole population we compared the 5 selected practices with the 7 unselected practices and the whole population (all 12 practices are listed in Appendix 4). Practices selected for this study did not have any significant differences with either the other 7 practices or the whole source population in terms of mean age, BMI and proportion of women (Table 2-2).

Table 2-2. Characteristics of practices selected for recruitment

	Selected practices	Other practices	All practices
Total number of responders	1662	3017	4679
Agreed to receive information	1284	2331	3615
Mean age (SD)	63.49 (10.07)	61.03 (9.91)	61.93 (10.04)
Proportion of women, (%)	765 (59.61)	1364 (58.55)	2130 (58.92)
Mean BMI (SD)	26.61 (5.00)	27.77 (5.49)	27.35 (5.35)
Prevalence of knee pain, (%)	735 (57.25)	1435 (61.58)	2169 (60.00)

Note: SD - standard deviation; BMI - body mass index.

The total number of responders to the KPIC baseline questionnaire in selected practices was 1662. Of these 1284 agreed to receive information about further projects, including 521 men and 763 women. A random sample of 250 men and 250 women, irrespective of knee pain status, were selected from each gender group to give a total sample of 500. Of the 500 selected participants 360 agreed to participate. A detailed breakdown of recruitment is presented in Figure 2-1. The characteristics of participants invited for the current study (n=500), and those who did reply (n=360) are shown in Table 2-3.

Table 2-3. Characteristics of the random sample from the general population

	Total (N=500)	Responders (N=360)	P-value*
Age (years), mean (SD)	63.77 (9.83)	64.70 (9.56)	0.0006
Women, n (%)	250 (50.00)	182 (50.42)	0.8745
BMI, mean (SD)	26.68 (4.99)	26.78 (4.97)	0.4757
Knee pain, (%)	244 (48.80)	187 (51.80)	0.2871
Current knee pain, (%)	138 (27.60)	109 (30.19)	0.2702
Current knee pain severity (NRS 0-10), mean (SD)	1.91 (2.88)	1.99 (2.86)	0.2914
Worsening of pain at one year**	49 (9.80)	35 (9.70)	0.9466

Note: * p-value for the difference between responders and the whole source population;
 ** - according to the Patient Global Impression of Change.

SD - standard deviation; BMI - body mass index; NRS – numerical rating scale (range 0-10).

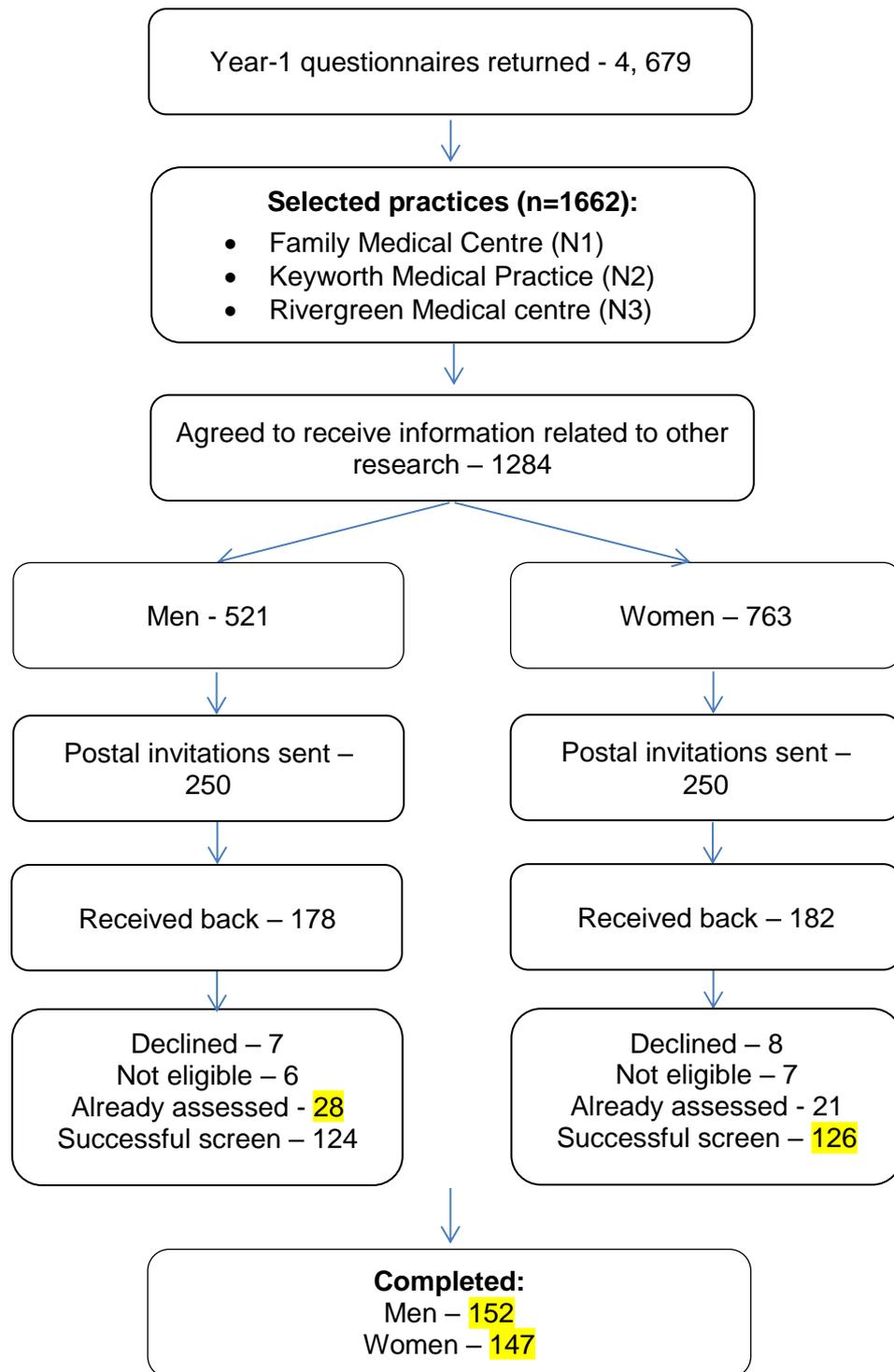


Figure 2-2. Recruitment of participants in the cross sectional study

Note: Not eligible – TKR (14), death (1); Response rate: 71.2% (178/250) in men, 72.8% (182/250) in women, 72% (360/500) pooled.

Please note that the number of questionnaire received (n=4679) is different from the number provided in the Figure 2-1 (n=4738) because the first was estimated at the time of study selection, whereas the latter reflects the final total number of questionnaire received (there were late replies).

2.4.2. Nested case-control study with both cross-sectional and follow-up data

Participants for this case-control study were selected from the baseline KPIC cohort according to current self-reported knee pain status. “Early knee pain” was defined as pain commencing within the past 3 years regardless of pain severity. Chronic “Established knee pain” was defined as moderate to severe knee pain of more than 3 years duration. Pain-free controls reported no knee pain within the past 5 years.

Selection for the “Early knee pain” group was undertaken from all participants who met inclusion criteria and agreed to participate in clinical assessments. Participants for the established knee pain and no knee pain groups were frequency matched with early knee pain participants by age (+/- 2 years) and gender. Random selection was undertaken if more than one participant was eligible for matching. In addition, all participants, who reported incident knee pain at one year and met inclusion criteria, were invited for clinical assessments. These participants were included in the “Early knee pain” group. A detailed breakdown of recruitment including three original groups recruited at baseline and also incident cases identified at one year is presented in Figure 2-3 and Figure 2-4.

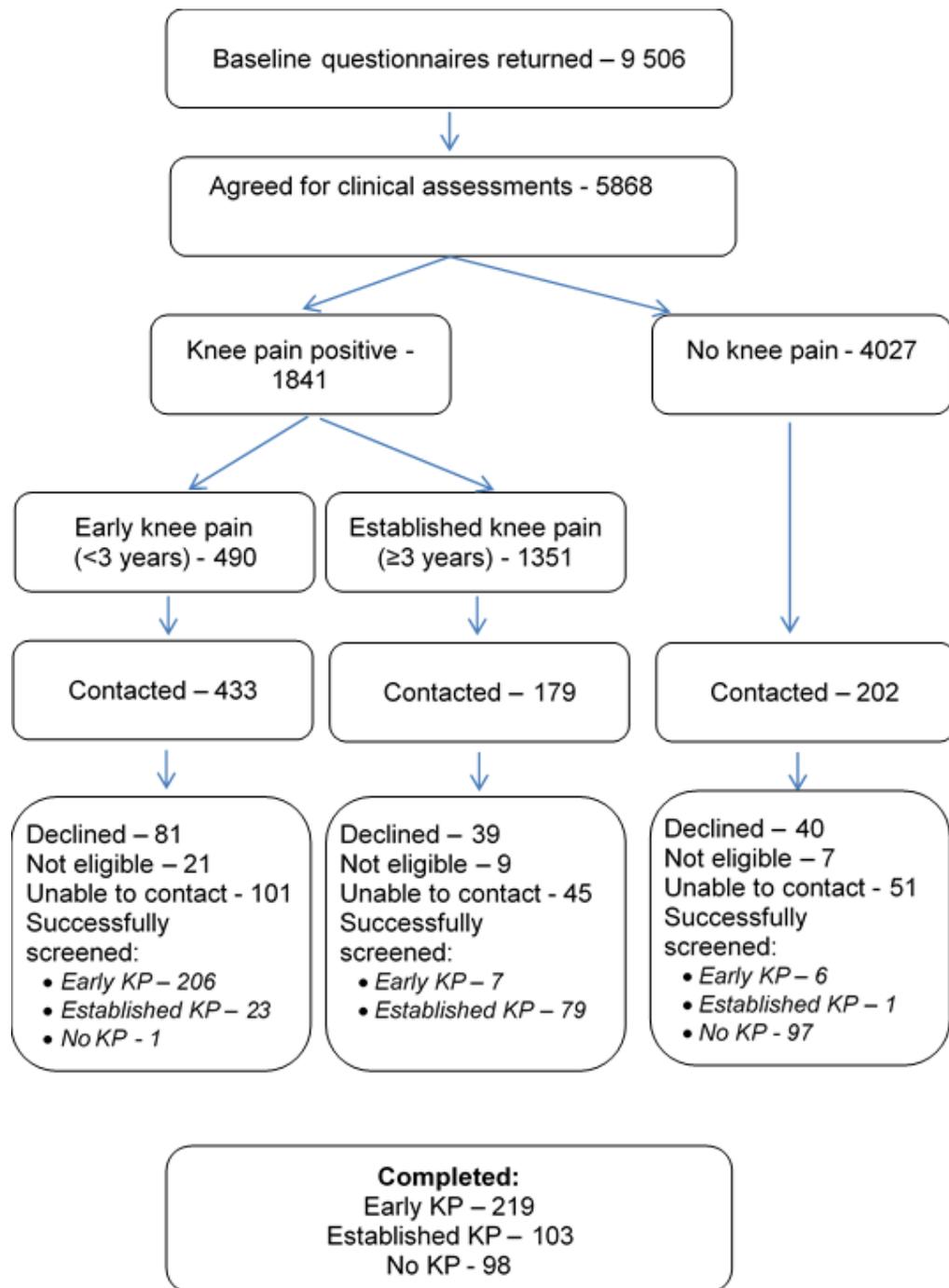


Figure 2-3. Recruitment of participants in the case-control study

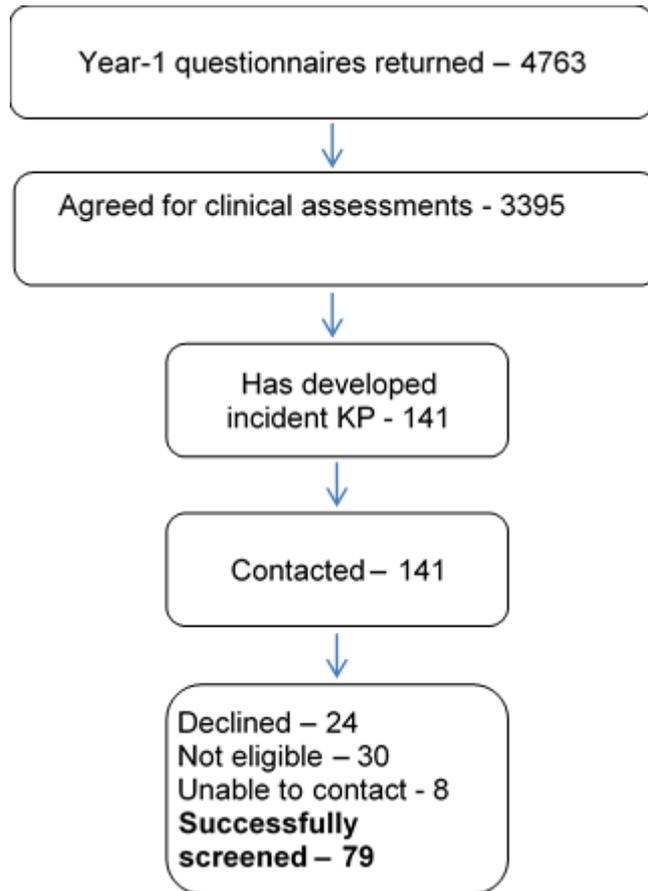


Figure 2-4. Recruitment of participants with incident knee pain

At baseline all participants had US, radiographic and muscle strength assessments (n=495). An identical follow-up US assessment was performed just on early knee pain participants approximately 12 months after their baseline assessment. Of 219 participants with early knee pain at baseline, 166 (76%) completed the 1 year follow-up US assessment. Those who attended the follow-up visit were similar to the “Early knee pain” group (Table 2-4).

Table 2-4. Characteristics of participants attended the follow-up assessment at one year

	Total (N=219)	Responders (N=166)	P-value*
Age (years), mean (SD)	60.28 (9.45)	60.90 (9.30)	0.0861
Women, n (%)	134 (61.19)	102 (61.45)	0.9482
BMI, mean (SD)	29.00 (5.60)	28.60 (5.08)	0.0652
Baseline current knee pain severity (NRS 0-10), mean (SD)	4.65 (2.43)	4.44 (2.39)	0.0213
Radiographic osteoarthritis, n (%)	49 (22.37)	40 (24.10)	0.5123
Worsening of pain**	32 (14.61)	27 (16.27)	0.5435

Note: * p-value for the difference between responders and the whole source population.

** - according to the Patient Global Impression of Change.

SD - standard deviation; BMI - body mass index; NRS – numerical rating scale (range 0-10).

After one year 181 (83%) participants with early knee pain and 74 (76%) participants with established knee pain completed the follow-up questionnaire. There was no difference between those who returned the questionnaire and the whole source population (Table 2-5).

Table 2-5. Characteristics of the responders to the follow-up questionnaire at one year among people with early and established knee pain recruited at the baseline

	Total (N=322)	Responders (N=255)	P-value*
Age (years), mean (SD)	60.04 (9.63)	60.94 (9.65)	0.0010
Women, n (%)	197 (61.18)	156 (61.18)	0.8376
BMI, mean (SD)	29.95 (6.05)	29.43 (5.61)	0.0023
Baseline current knee pain severity (NRS 0-10), mean (SD)	5.53 (2.67)	5.30 (2.64)	0.0021
Radiographic osteoarthritis, n (%)	98 (30.43)	83 (32.94)	0.3814

Note: * p-value for the difference between responders and the whole source population.

SD - standard deviation; BMI - body mass index; NRS – numerical rating scale (range 0-10).

2.4.3. Cross-sectional study for contribution of central vs peripheral risk factors (including synovial changes detected on US) to knee pain and the role of synovitis in different types of knee pain

This cross-sectional study included 495 participants from the case-control study and 241 participants from the cross-sectional US study described previously (Section 2.4.1 and Section 2.4.2). As both studies were recruited from the same cohort, there was an overlap. For example, of 299 participants included in the cross-sectional study, 20 participants were already assessed as they reported incident KP at one year, and 29 participants were already assessed as part of the follow-up assessment for people in the Early KP group (n=219 on baseline, and n=166 at follow-up). Therefore, a total of 250 participants were successfully screened for the cross-sectional study. However, 9 of 250 participants were already assessed at baseline as part of the case-control study. These 9 participants were re-assessed for the cross-sectional study. For these participants with two data points available ("Early knee pain" group) the baseline data were chosen for further analysis. Therefore, only 241 out of 299 participants from the cross-sectional study were selected for further analysis.

All participants were categorised according to the presence/absence of knee pain, ROA and WSP. For the further analysis 5 subgroups were identified:

- Subgroup 1 – participants with knee pain, ROA and WSP;
- Subgroup 2 – participants with knee pain and ROA but not WSP;
- Subgroup 3 – participants with knee pain and WSP but not ROA;

- Subgroup 4 – participants with knee pain but not ROA or WSP;
- Controls – pain-free individuals without ROA and WSP.

The detailed breakdown is presented in Figure 2-5.

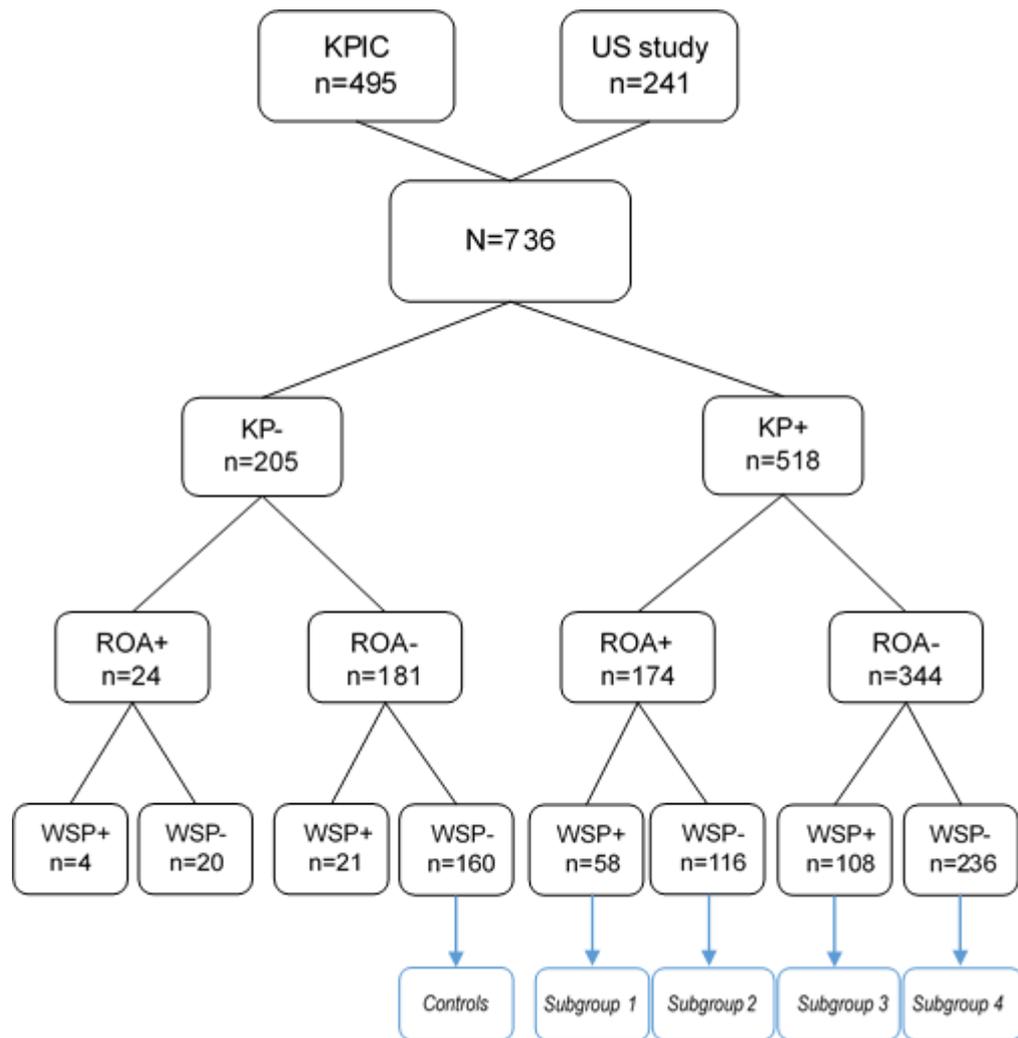


Figure 2-5. Breakdown of recruitment

Note: KP – knee pain defined as pain in or around a knee on most days for at least a month. ROA - Radiographic osteoarthritis defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral). WSP - Concurrent pain experienced within the past 4 weeks axially, above and below the waist, and on both sides of the body (ACR criteria) self-reported using a diagrammatic manikin.

2.5. Outcome/exposure measures

The information about outcomes and exposures was obtained from the questionnaire and subsequent clinical assessments. A summary of clinical assessments available for all three studies is provided in Table 2-6. US and radiographic assessments were blinded to participant characteristics including pain status.

Table 2-6. Summary of clinical assessments

Measure	Description	Cross sectional	Case control	
			Baseline	Follow-up
Anthropometric measures	Weight	+	+	+
Muscle strength	Hip abductor and quadriceps strength		+	+
Radiographic assessment	Bilateral tibio-femoral and patello-femoral radiographs	+	+	
Ultrasound assessment	Effusion, synovial hypertrophy and Doppler signal	+	+	+

2.5.1. Pain measures

Knee pain was defined as pain in or around a knee on most days for at least a month (Nguyen et al., 2011, O'Reilly et al., 1996).

Current knee pain was defined as pain on most days of the past month. Pain intensity in the past month was assessed on a 0-10 numerical rating scale (NRS).

Incident knee pain was defined as no knee pain at baseline but knee pain reported at follow-up.

Worsening of knee pain was defined using the following question: “Since it has started, do you think the severity of your knee pain has overall...greatly improved/ slightly improved/ remained the same/ worsened” (Patient Global Assessment (PGA)) (Dworkin et al., 2005).

The index knee was defined as the only (participants with unilateral knee pain) or most painful knee (participants with bilateral knee pain). For individuals with equal bilateral knee pain or for those without knee pain the index knee was selected randomly.

Knee pain was classified as **neuropathic-like and non-neuropathic like pain** using a modified version of the PDQ. Neuropathic-like knee pain was defined when the PDQ score was 19 and above (Hochman et al., 2011, Freynhagen et al., 2006).

Knee pain was also classified as **intermittent and/or constant** using the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire (Hawker et al., 2008). Constant pain was defined as a continuous experience of pain, aching or discomfort, whereas intermittent pain was characterised as being severe but short-lived, including pain triggered by a specific activity or movement and relieved by rest, and also spontaneously occurring pain which resolves completely (Hawker et al., 2008). A summative score for each sub-scale (intermittent and constant) was calculated and standardised into 0-100 scale according to the User’s Guide for the Measure of ICOAP (2007). Tertiles were calculated

separately for intermittent and constant subscales using the baseline scores of people with knee pain.

2.5.2. Self-reported risk factors

- **Demographics:** age, gender, and height were self-reported and obtained from the postal questionnaire.
- **WSP** was identified using a diagrammatic manikin (Appendix 5) and was defined as concurrent pain experienced within the past 4 weeks axially, above and below the waist, and on both sides of the body according to the ACR criteria (Wolfe et al., 1990). Current knee pain was not counted for this.
- **The Hospital Anxiety and Depression Scale (HADS) and Pain Catastrophizing Scale (PCS) scores** were summated as recommended (Mykletun et al., 2001, Sullivan et al., 1995). A score on HADS-A and HADS-D ≥ 8 was used as an indicator of anxiety and depression (Mykletun et al., 2001). Tertiles of the PCS score were calculated from the whole sample including those with and without knee pain.
- **Nodal OA** was determined using a validated line diagram and classified as present in those reporting nodes (Heberden's or Bouchard's) on at least two rays of both hands (Zhang et al., 2009, O'Reilly et al., 1999).
- **2D:4D** finger ratio (index to ring finger length ratio) was self-reported using a validated line-drawing instrument in the postal

questionnaire (Ingham, 2010, Zhang et al., 2008). Finger length patterns were visually classified as, Type 1 (index finger longer than ring finger), Type 2 (index finger equal to the ring finger $2D=4D$) and Type 3 (index finger shorter than the ring finger).

- **A major/significant knee injury** was defined as a history of knee injury that required seeing a doctor (leg fracture was asked separately).
- **Self-reported frontal plane knee alignment** was assessed using a validated line diagram instrument (Ingham et al., 2010). Participants separately reported their current and early adult life (aged in their 20's) knee malalignment as severe varus, mild varus, straight legs, mild valgus, or severe valgus for right and left knees. **Constitutional malalignment** was defined as a bilateral varus/valgus malalignment when the participant was aged in their 20's.

2.5.2.1. Other factors

- **Analgesics:** Use of prescribed and/or over-the-counter **analgesics** (e.g. paracetamol; NSAIDs, including selective inhibitors of cyclooxygenase-2 (COX-2); opioids) was self-reported.
- **Comorbidities:** History or current evidence of comorbidities was recorded for the following conditions: cardiovascular disease (high cholesterol*, heart attack*, angina*, hypertension*), lung disease (chronic obstructive pulmonary disease (COPD), asthma,

idiopathic pulmonary fibrosis), endocrine disease (diabetes*, underactive/overactive thyroid, thyroiditis), non-restorative pain disorders (irritable bowel syndrome*, fibromyalgia*, chronic fatigue syndrome*), liver disease (liver cirrhosis, hepatitis, non-alcoholic fatty liver disease), chronic kidney disease/failure (CKD), central nervous system disorders (stroke*, multiple sclerosis), chronic rheumatic conditions (RA, lupus, psoriatic arthritis, ankylosing spondylitis), and gout. In the questionnaire a list of specific conditions (marked above with an asterisk) and an open “others” question were provided. All conditions were then grouped according to the system as listed above. The comorbidity count was calculated as a total number of affected systems (from 0 to 9). The presence of comorbidity in any system was additionally recorded as absent/present.

- **High risk occupation** was classified based on published evidence (Palmer (2012), Appendix 6). Each listed occupation per individual was analysed and the data dichotomised into high- or low-risk groups.

2.5.3. Clinical assessments

2.5.3.1. US assessment protocol

US examination of both knees was performed by two assessors (Dr. Michelle Hall and Dr. Aliya Sarmanova) for the KPIC baseline and follow-up study. A single assessor (AS) undertook the US assessments for the study on the general population. All assessments used the same Toshiba Aplio SSA-770A machine with a multi-frequency (7-12 MHz) linear array transducer.

A standardised research protocol was developed according to recommendations from the EULAR Research Group (D'Agostino et al., 2005, Backhaus et al., 2001) and the European Society of Musculoskeletal Radiology (Martinoli, 2010). Anterior aspect of the knee was assessed in a supine position with knee flexion of approximately 20-30° and voluntary quadriceps contraction (Ike et al., 2010). The 30° flexed position, which is the most sensitive position to detect fluid in knee joints, was obtained by placing a small roll underneath the knee as reported by Mandl et al. (2012). Medial and lateral aspects of the knee were assessed with the leg externally and then internally rotated (Bianchi and Martinoli, 2007). A wide multi-planar approach including both longitudinal and transverse transducer planes was applied to assess the supra-patellar, and the medial and lateral tibio-femoral spaces of the knee (Figure 2-6, 2-7, 2-8). To minimise pressure between the transducer and the participant's skin a generous amount of scanning gel was applied. A comfortable position for both the participant and assessor was achieved to minimise motion artefacts during US assessment.

Assessment included both Grey-scale (B-mode) and Power Doppler modes. Focus points and image magnification of the area of interest were adjusted manually to obtain better visualisation. The parameters of Power Doppler were also adjusted during the examination to achieve optimum sensitivity. Pulse repetition frequency (PRF) ranged between 5-13 MHz and Power Doppler gain was manually increased to fill the box with colour (random noise), then reduced until the background signal was removed. Power Doppler mode provides information on vascularity overlaid on the B-mode.

Pathological US-detected changes were defined according to definitions accepted by the OMERACT-7 Special Interest Group (Wakefield et al., 2005). The depth of synovial thickness and effusion were each measured on a continuous scale at their maximal diameter in millimetres using the longitudinal axis. Absolute value of effusion and hypertrophy were also dichotomised as absent if $< 4\text{mm}$ and present if $\geq 4\text{mm}$ according to EULAR recommendations (D'Agostino et al., 2005). Power Doppler assessment was focused on areas of synovial hypertrophy and positive PDS was recorded as absent or present. Only one value per joint was recorded for each US feature (maximum value across three areas scanned).

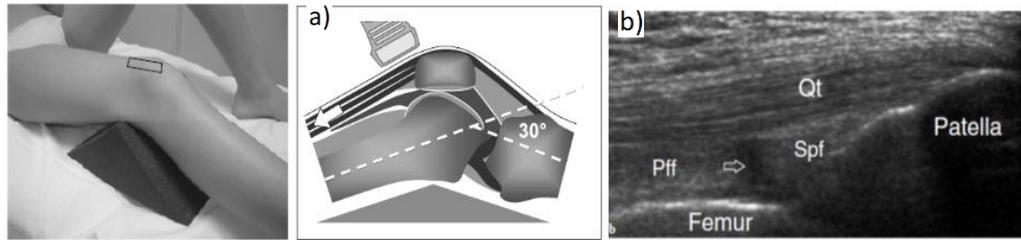


Figure 2-6. Assessment of the suprapatellar region on ultrasound.

Note: suprapatellar synovial recess (arrow) with the suprapatellar (Spf) and pre-femoral (Pff) fat pads. a. Schematic drawing. b. Long-axis US image over the quadriceps tendon (Qt). (Bianchi and Martinoli, 2007), permission granted.



Figure 2-7. Assessment of the medial tibio-femoral space of the knee on ultrasound

Note: a. Coronal US image over the medial collateral ligament with b. schematic drawing correlation demonstrates this ligament is composed of two definite superficial (straight arrows) and deep (arrowheads) layers. A synovial bursae lies between the two ligaments components and isn't visualised in normal conditions. Meniscus (asterix), femur (Fem) and Tibia (Tib) respectively. (Bianchi and Martinoli, 2007), permission granted.

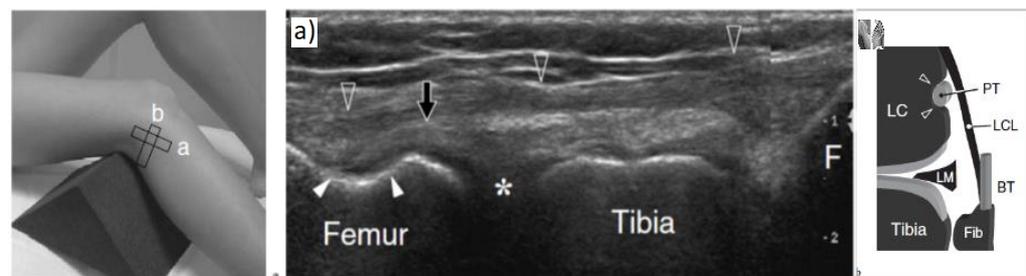


Figure 2-8. Assessment of the lateral tibio-femoral space of the knee on ultrasound

Note: a. Coronal US image over the lateral collateral ligament (open arrowheads) with b. schematic drawing correlation demonstrates the cord-like lateral collateral ligament (LCL) joining the lateral femoral condyle (LC) and fibula (Fib). Meniscus (asterix, LM), popliteus tendon (PT) and tendon of biceps muscle (BP), respectively. (Bianchi and Martinoli, 2007), permission granted.

2.5.3.2. Radiographic assessment

Bilateral weight-bearing semi-flexed posterior-anterior tibio-femoral views using a Rosenberg template, and 30° flexion skyline patello-femoral views were undertaken using standardised protocols. All radiographs for this study were obtained in PACS electronic format and analysed using HIPAX Dicom software. The weight-bearing semi-flexed posterior-anterior view has been shown to have better sensitivity to define JSN (Duncan et al., 2015) and therefore is recommended by OARSI for evaluating tibio-femoral OA (Hunter et al., 2015). The skyline view is preferred to the lateral patello-femoral view since it provides a clearer view of joint space width and permits determination of medial versus lateral narrowing in the patello-femoral joint (Cicuttini et al., 1996, Hunter et al., 2015).

All knee radiographs were scored for osteophytes and JSN according to their compartmental location (lateral or medial compartment) in both TFJ and PFJ (Figure 2-9) using the Nottingham LDLDA score (Nagaosa et al., 2000, Wilkinson et al., 2005). Additionally, the K&L score, presence or absence of CC, attrition and subluxation in both TFJ and PFJ were recorded.

Scoring by the LDLDA scoring system was performed using an interval line diagram atlas with separate sets of line drawings for JSN for men and for women (scoring sheets are located in Appendix 7). The grades for JSN and osteophytes (from 0 to 5) increase in strictly geometric (interval) fashion (for example see Figure 2-10). The atlas also includes grades for uncommon shapes of tibial and femoral osteophytes

and negative scores indicating joint space widening (grade -1) (Nagaosa et al., 2000, Wilkinson et al., 2005).

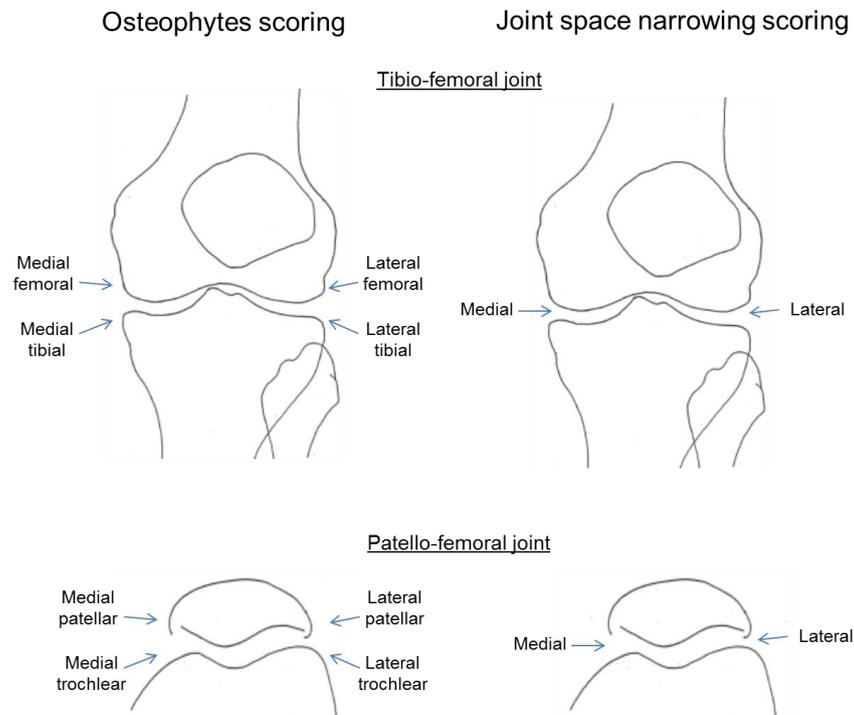


Figure 2-9. Compartments assessed for the presence of structural changes according to the Nottingham logically derived ordinal line diagram atlas (Nagaosa et al., 2000, Wilkinson et al., 2005)

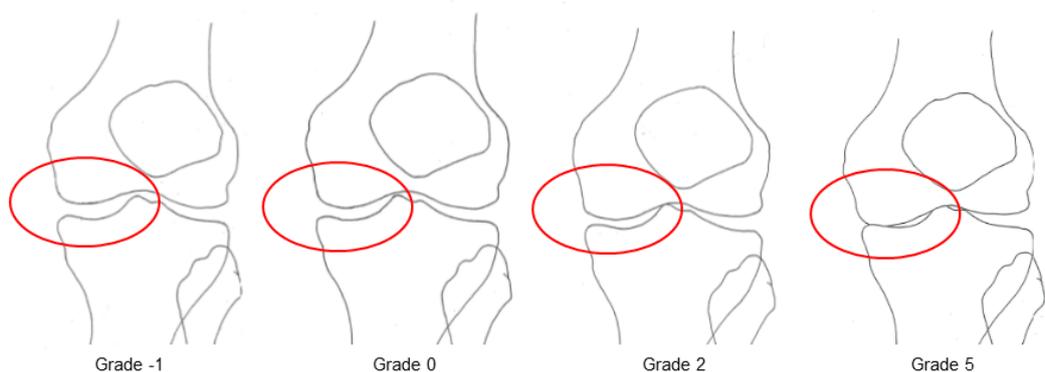


Figure 2-10. Medial joint space narrowing scoring example for the tibio-femoral joint in women according to the Nottingham logically derived ordinal line diagram atlas (Nagaosa et al., 2000, Wilkinson et al., 2005)

The scores for osteophytes and JSN in both TFJ and PFJ (medial and lateral compartments), ignoring -1 values for JSN (i.e. joint space widening), were summated as a **global score** for each knee. The global score reflects the multi-compartmental severity of radiographic changes (van der Esch et al., 2014)

Presence of ROA was defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral). This definition of definite osteophyte and definite narrowing is in accord with the pathological definition of OA which requires both definite focal loss of hyaline cartilage and definite associated bone change (Braun and Gold, 2012).

Scoring by K&L system was performed according to well-known definitions and the “Atlas of individual radiographic features in OA, revised” (Figure 2-11, Altman and Gold (2007)).

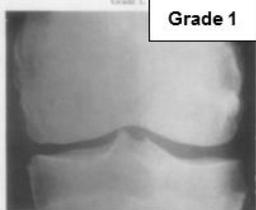
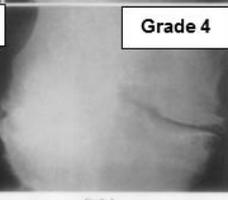
		Grade	Description
		Grade 0	No changes
		Grade 1	Doubtful narrowing of the joint space and possible osteophyte lipping
		Grade 2	Definite osteophytes and possible narrowing of the joint space
		Grade 3	Moderate multiple osteophytes, definite narrowing of the joint space, and some sclerosis, and possible deformity of the bone ends
		Grade 4	Large osteophytes, marked narrowing of the joint space, severe sclerosis and deformity of the bone ends

Figure 2-11. Kellgren and Lawrence radiographic knee OA classification (Kellgren and Lawrence, 1957)

2.5.3.3. Muscle strength assessment

Maximal isometric strength of the quadriceps muscles was tested using a manual muscle tester (MMT) (Nicholas Manual Muscle Tester; Lafayette Instruments) three times on each leg and then the mean value was calculated for each side (Hayes and Falconer, 1992). Participants were sitting upright on the edge of a stable four-legged chair (no arm rests) with knees flexed to 90° and were asked to push their leg as hard as possible against the MMT held against the distal tibia above the ankle joint in an attempt to raise their leg forwards. The MMT displays the maximal force generated in kilograms. Normal tertiles of the quadriceps and hip abductor strength were calculated from the pain-free controls (n=98, KPIC case-control study at baseline).

2.6. Training and agreement exercises

2.6.1. US assessment

Sonographic training for knee US was undertaken under the supervision of an experienced investigator, Dr. Michelle Hall (MH), a lecturer at the Faculty of Medicine & Health Sciences, University of Nottingham. One to one teaching sessions were focused on the principles of musculoskeletal US, the approach to the US equipment, patient positioning, transducer alignment, and also development of practical skills including multi-planar scanning, detection of effusion, synovial hypertrophy, bursitis and osteophytes, use of power and colour Doppler, optimising images and recognising and minimising artefacts. Additional resources used during the teaching programme included textbooks, atlases, papers, and video materials on musculoskeletal US (Kane et al., 2005, Backhaus, 2009, Friedman et al., 2001, Kane et al., 2004, Martinoli and Bianchi, 2007, Backhaus et al., 2001, Martinoli, 2010, Wakefield et al., 2005, Torp-Pedersen and Terslev, 2008).

The total duration of US training was over 30 hours received from November 2014 until the end of January 2015. At the end of the training period the competency of the trainee was assessed by the trainer and results were satisfactory (example images are presented in Appendix 8). A similar training approach has been shown to achieve competency within a similar training period (Filippucci et al., 2003).

In the ***inter-observer reliability*** exercise two assessors (MH and Aliya Sarmanova (AS)) blindly, independently and consecutively carried out on the same day the greyscale and Power Doppler US examination of both knees of 16 individuals (including participants from the KPIC study as well as additional volunteers). ***Intra-observer reliability*** was tested for the study assessor (AS) by scanning the knees of 4 volunteers (8 knees) on two separate days within a seven day period. The scanning technique was standardised.

2.6.2. Scoring radiographs

Training for knee radiographic assessment was undertaken under the supervision of an experienced investigator (Sally Doherty (SD), Senior Research Nurse at the Faculty of Medicine & Health Sciences, University of Nottingham, who had scored all OA research radiographs in Academic Rheumatology over the previous 15 years). The training period was from November 2015 to January 2016 and included one-to-one sessions and a self-teaching approach. More than 100 bilateral knee radiographs were scored by the trainee and approximately 30 of them were double-checked by the trainer and fully discussed.

Inter-observer agreement testing was performed between two observers who independently and consecutively scored radiographic images of the sampled participants:

- between trainer and trainee (SD and AS) at the end of the training period to assess the competency of the trainee;

- between two investigators performing radiographic scoring for the KPIC study (Dr. Gwen S Fernandes (GSF) and AS) after training, before and during the scoring of images for the KPIC study.

For intra-observer comparison the same radiographic images were scored by the observer (AS) on two separate days within a seven day period.

Image selection. Radiographic images were selected from two large population-based cohorts: the KPIC study with a total number of 420 participants and the Risk of Knee pain and Knee OA in Retired Professional Footballers study (Arthritis & Football study, n=300). The KPIC study mainly focused on people with early knee pain so the prevalence of structural abnormalities on radiographs was expected to be low. In contrast, the majority of participants from the Arthritis & Football study showed from moderate to severe structural abnormalities on radiographs. Therefore, stratified randomisation was applied to select participants from the available radiographic images in order to cover a wide range of radiographic severity.

Three sets of bilateral knee radiographs were selected. The first sample of 23 participants included 10 participants from the KPIC study and 13 participants from the Arthritis & Football study. 44 knees from this sample were available for assessment (2 knees had TKR and were excluded from the analysis). The second sample comprised 21 participants (10 from the KPIC study and 11 from the Arthritis & Football study) giving a total of 40 knees (2 knees had TKR and were excluded from the

analysis). The third sample comprised 20 participants (10 from the KPIC study and 10 from the Arthritis & Football study) giving a total of 40 knees.

Agreement for osteophytes and JSN grading was calculated separately for the TFJ and PFJ and for the whole knee.

2.7. Statistical analysis

2.7.1. Sample size and power calculation

2.7.1.1. Sample size for the agreement test

Sample size for kappa-statistic when there are two unique raters (inter-observer agreement) was calculated using the “sskdlg” package in Stata software (Reichenheim, 2001, Cantor, 1996). The estimation is based on the asymptotic variance presented by Fleiss (1969).

US assessment. If both raters are expected to find a prevalence of 50% of the event of interest and the expected kappa statistic is 0.7 (substantial agreement) with precision of 0.3 (range 0.4-1.0), this reliability study will need at least a sample of 23 knees. Figure 2-12 provides a graphical display of the absolute precision for a range of prespecified sample size (from 0 to 40).

Radiographic assessment. If the prevalence of the structural abnormalities on radiographs is expected to be 70% and the expected kappa statistic is 0.8 (perfect agreement) with a precision of 0.2 (range 0.6-1.0), this reliability study will need at least a sample of 35 knees (Figure 2-13).

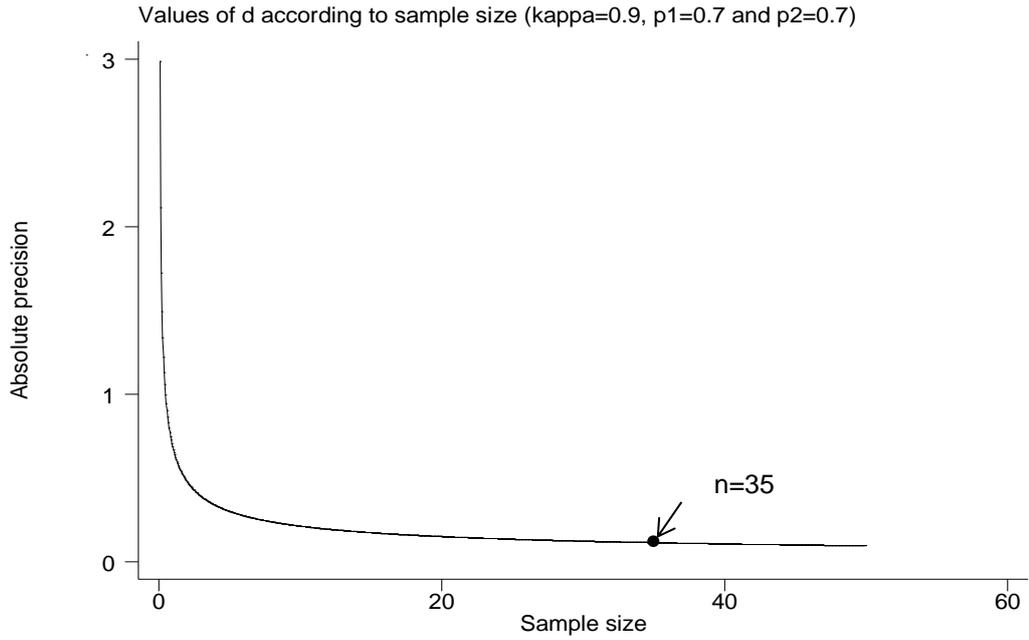


Figure 2-12. Sample size for agreement on ultrasound assessment

A graphical display of the absolute precision for a range of pre-specified sample size (from 0 to 60)

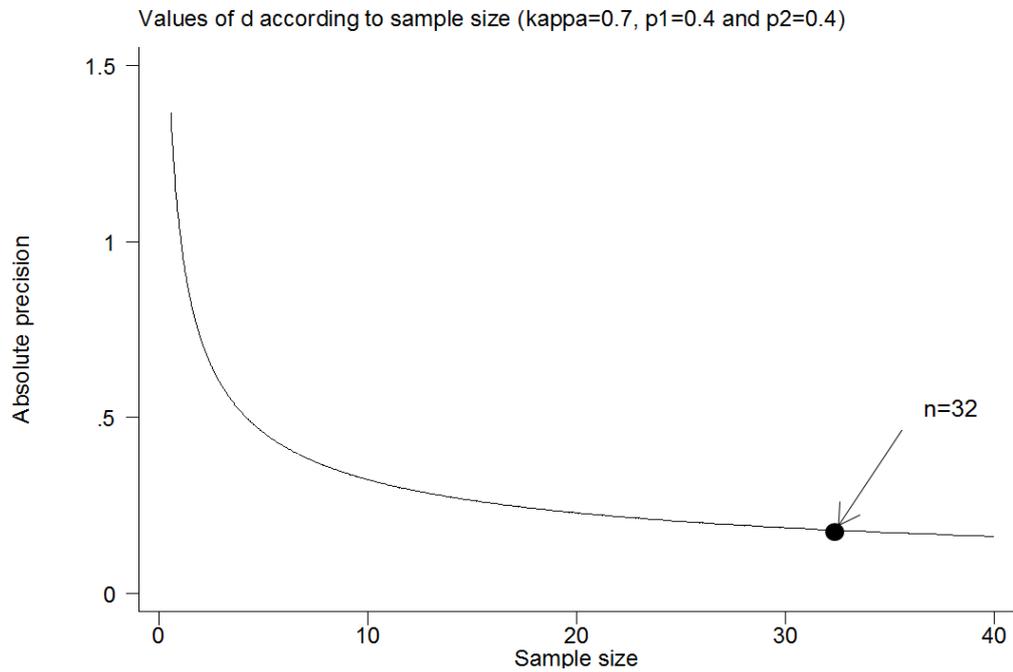


Figure 2-13. Sample size for agreement on scoring radiographs

A graphical display of the absolute precision for a range of pre-specified sample size (from 0 to 40).

2.7.1.2. Sample size for the cross sectional study

Sample size was calculated using the formula for a single cross-sectional study:

$$\text{Sample size} = \frac{Z_{1-\alpha/2}^2 p(1-p)}{d^2}$$

Where $Z_{1-\alpha/2}$ is standard normal variate (at 5% type I error is equal to 1.96); p – expected proportion in population; d – absolute error or precision (Charan and Biswas, 2013).

Although a population-based study conducted by Abraham et al. (2014) reported a prevalence of US-detected effusion of 24% in people aged 61-63 years old, we assumed that the positive rate of US effusion in the broader age range of KPIC participants (i.e. over 40 years old) would be lower, i.e., $p=10\%$. The sample size required for this cross sectional study varied from 138 to 384 depending on the error margin ($d=3-5\%$). This gave a power of $\geq 90\%$ and a type I error of 5% for the study.

2.7.1.3. Sample size for the case-control study

An unbalanced (2:1:1 for “Early KP”, “Established KP”, “No KP”) one-way analysis of variance (ANOVA) design was applied to ensure sufficient early KP cases for the cohort study. The effect sizes reported from Hall et al (2014) were used to calculate sample size. Considering 90% power with 5% type I error, 80 participants were required for the primary analysis to detect the minimum difference between the 3 groups (40:20:20). The full sample of 495 participants (298:103:94) was included to allow regression analysis for multiple covariates.

2.7.1.4. Sample size for the follow-up study

Limited evidence is available for the association between changes in pain and changes in effusion or synovial hypertrophy. Therefore, the **sample size for the correlation analysis** was calculated assuming that there is at least a small correlation ($r=0.3$) between changes in pain and changes in US values. 112 participants are required with 90% power and less than 5% type I errors. **For the risk prediction model**, sample size was calculated based on the logistic model with one predictor adjusted with three covariates (e.g., age, gender and BMI) assuming that there is a correlation between them ($r=0.3$). The study was powered for an OR as small as 1.7 for synovial hypertrophy assuming that the probability of worsening of knee pain lies between 14% and 19% (Jinks et al., 2008, Ingham et al., 2011b). With 80% power and less than 5% type I errors, 195 participants are required.

2.7.2. Reproducibility tests

The amount of agreement means that we can reject the hypothesis that observers are making their readings randomly. We used the unweighted kappa-statistic for dichotomous data, the concordance correlation coefficient for continuous data and Bland and Altman's plot to inspect data pattern. Reproducibility was tested to determine the intra- and inter-observer agreement of key US measures (knee effusion, synovial hypertrophy, PDS) and x-ray scoring. All assessments were independent, standardised and blinded to participant characteristics including pain status.

Kappa-statistics. The magnitude of agreement on dichotomous data was measured using the unweighted kappa-statistic measure (Viera and Garrett, 2005). For ordered categorical values the weighted kappa-statistic measure was used (Armitage et al., 2002). Weights were assigned equally, which means that the importance of disagreements in measuring different grades was equal. A numerical rating of kappa was interpreted according to accepted criteria presented in Table 2-7 (Landis and Koch, 1977) and 95% CI were reported (Reichenheim, 2004).

Table 2-7. Strength of agreement – kappa statistics

Value of kappa	Strength of agreement
0-0.2	Slight
0.2-0.4	Fair
0.41-0.6	Moderate
0.61-0.8	Substantial
0.81-1.0	Almost perfect

Concordance correlation coefficient. Inter-observer agreement of original continuous data was calculated using Lin's concordance correlation coefficient (Lin, 1989). This is a combined measure of precision and accuracy of assessment based on the deviation of obtained data from the line of perfect concordance (Steichen and Cox, 1999, Steichen and Cox, 2002). If readings are in perfect agreement and do not deviate from the 45° line the concordance correlation coefficient is equal to 1. The concordance correlation coefficient less than 0.5 indicates poor reliability, between 0.5 - 0.75 moderate reliability, between 0.75 - 0.90 good reliability and > to 0.90 excellent.

The concordance correlation coefficient (r_c) also combines Pearson's correlation (r) as a measure of accuracy and a bias correction factor (c_b) as a measure of precision: $r_c = r c_b$, $0 < c_b \leq 1$. However, r_c is either equal to or closer to 0 than Pearson r .

In specific cases the concordance correlation coefficient is comparable to another widely used agreement measure such as the intra-class correlation coefficient (ICC). For example, the results are the same or have similar values in the case of two observers and if the two-way fixed-effect ANOVA model is chosen to calculate ICC (Barnhart et al., 2007, Carrasco and Jover, 2003). However, the ICC can be criticised because it is less suited for data with repeated measures (for intra-observer agreement) (Barnhart et al., 2007, Chen and Barnhart, 2013).

Bland and Altman plots. There are several graphical methods to examine the distribution of data, the relationships between obtained values, and to identify outliers. Bland and Altman plots have been shown to be more effective than standard scatter plots (Hanneman, 2008). The difference between each pair of readings, also called bias, is plotted on the y-axis (1st observer minus 2nd observer, or readings at day 1 minus readings at day 2) against their mean values on the x axis. The confidence limits (95% limits of agreement) indicate the total error including the bias and random error.

A visual display provides the size, direction, and range of the differences between observers, and also whether bias is consistent across the range of measurements. The closer the mean difference is to 0 and the smaller the 95% limits of agreement, the better the agreement. The positive bias (when the dash line is above or below zero) quantifies how much higher or lower values are with the 1st observer compared with the 2nd observer (Steichen and Cox, 1999, Hanneman, 2008).

The methods used to measure agreement on different outcomes are summarised in Table 2-8. Statistical analysis was undertaken in Stata SE software V13.1 (StataCorp LP, College Station, TX, USA) (Nyaga et al., 2014, Chaimani et al., 2014).

Table 2-8. Summary of methods used to analyse agreement on categorical and continuous data.

Measure	Statistics
Ultrasound	
Effusion (in mm)	Concordance correlation coefficient
Synovial hypertrophy (in mm)	Concordance correlation coefficient
Effusion ≥ 4 mm (present/absent)	Unweighted kappa
Synovial hypertrophy ≥ 4 mm (present/absent)	Unweighted kappa
Doppler signal (present/absent)	Unweighted kappa
Radiographs	
Osteophyte grade (from 0 to 5)	Weighted kappa
Joint space narrowing grade (from -1 to 5)	Weighted kappa
Kellgren & Lawrence grade (from 0 to 4)	Weighted kappa
Joint space width (in mm)	Concordance correlation coefficient
Radiographic osteoarthritis (present/absent)	Unweighted kappa

2.7.3. Descriptive analysis and basic statistics

All continuous data were checked for the assumption of normality. For normally distributed variables measures of central tendency are presented as the mean and the SD. Although some variables (such as BMI, depth of effusion and synovial thickness) were moderately skewed, descriptive characteristics were presented as mean and SD according to the central limit theorem, that is, when sample size increases, the data for these measures tend to be normally distributed (McDonald, 2014). Attempts were made to transform (log-transformation, square and square-root transformation) right-skewed data (for example, depth of synovial effusion, Nottingham LDDA scores) and after transformation data were tested for normality. If transformation was successful, parametric tests were used. If transformation was not successful, non-parametric tests were used.

Comparison of two categorical variables was performed using chi-square (χ^2) test if groups were independent and the expected value of the cell was ≥ 5 in at least 80% of the cells (McHugh, 2013, Armitage et al., 2002). If the expected value of the cell was < 5 in at least 80% of the cells Fisher's exact test was used.

Comparison of two continuous variables was performed using t-test. If a continuous variable was normally-distributed and comparison was made between independent groups (for example, mean age between responders and non-responders), a two sample t-test for independent groups was used (Armitage et al., 2002). If a continuous variable was

normally-distributed but comparison was made between dependent groups (for example, NRS pain score at baseline and at one year), then a paired t-test was used (Armitage et al., 2002).

The Cochran-Armitage test was used to examine trend across the three groups for categorical and continuous data (Margolin, 2004, Agresti and Kateri, 2011). We used “proc MULTTEST” with multiplicity adjustment using bootstrap in SAS (Dmitrienko et al., 2005).

Comparison of the proportion in a sample and the proportion in the complete population was performed to examine whether there is a difference between responders and the whole source population. For categorical (binary) variables, firstly, the proportion of the variable of interest in the whole source was calculated. Secondly, the proportion responding yes in the subset was compared to the known proportion responding yes in the source population using χ^2 test (support)(SAS software support usage note 22783). For continuous variables analysis of means (ANOM) was used (Westfall et al., 2011). ANOM estimates the difference between a given subset mean and the simple average of the population from which the subset was derived.

2.7.4. Establishing normal range and an optimal threshold

The results of a diagnostic test can provide an answer to two important questions such as [1] whether this result lies within a range of values in a healthy population (***normal range***) and [2] whether it corresponds with a specific level of risk or probability for the presence of a certain disease (***decision limits***) (Ceriotti and Henny, 2008). While the normal range is simply a statistical definition of the biological variability of the population, for some diagnostic tests it is more important to refer to the decision limits defined on the basis of analysis of clinical outcomes between normal range and disease (i.e. abnormal range) (Ceriotti and Henny, 2008, Murphy and Abbey, 1967).

2.7.4.1. Normal range

The reference interval or normal range is an interval between, and including, two reference limits corresponding to 95% of the population of healthy subjects (Ceriotti and Henny, 2008). In this study the upper reference limit (95% quintile) for effusion and synovial hypertrophy was calculated in the healthy sample (no current KP and no ROA). Quintiles were calculated using the distribution-free method ("proc UNIVARIATE CIPCTLDF", SAS) with corresponding 95% CI (Hahn and Meeker, 2011). A schematic representation of the reference interval with the upper reference limit and corresponding 95% CI is shown in Figure 2-14.

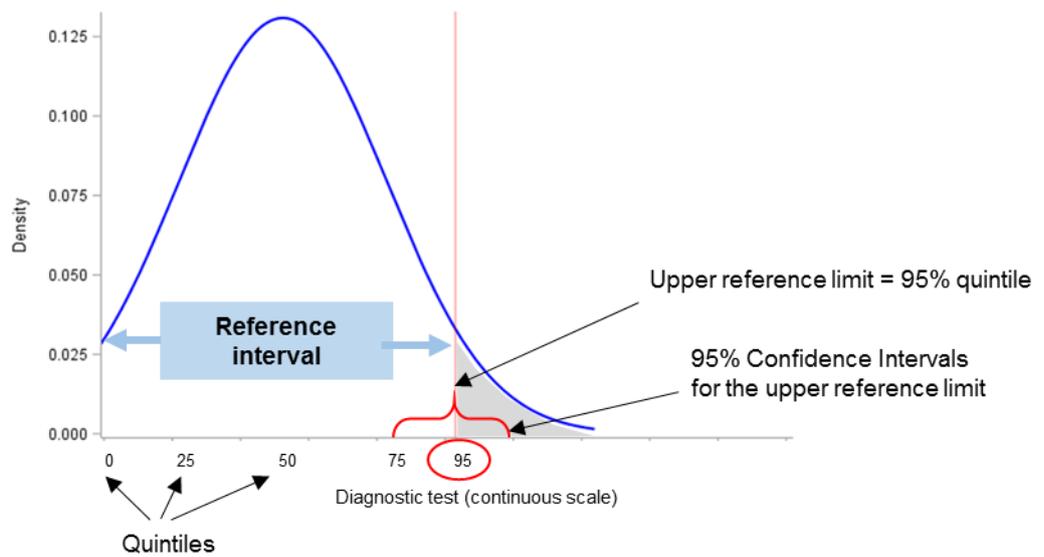


Figure 2-14. Schematic representation of the reference interval and upper reference limit with its confidence intervals

2.7.4.2. Optimal threshold

The discrimination ability (i.e. ability to separate cases and controls) of each synovial change was determined in a case control study, where people with KP and ROA were classified as cases and those without were classified as controls. Because both effusion and synovial hypertrophy were different between men and women, the diagnostic accuracy was examined in men and women separately.

The discrimination ability was examined using the following measures of diagnostic accuracy:

- *Sensitivity* is the proportion of participants with outcome correctly classified as 'diseased'.
- *Specificity* is the proportion of participants without outcome correctly classified as 'non-diseased'.
- *False positive probability (FPP)* is the proportion of positive test results in true negative cases.
- *False negative probability (FNP)* is the proportion of negative test results in true positive cases.
- *The likelihood ratio of a positive test result (LR+)* is sensitivity divided by 1-specificity. It describes how the probability of disease shifts when the finding is present.
- *The likelihood ratio of a negative test result (LR-)* describes how the probability of disease shifts when it is absent (1-sensitivity divided by specificity). The magnitude of the LR (range from 0 to infinity) suggests

how strongly a given test result will raise or lower the likelihood of disease (McGee, 2002).

- A ROC curve is a plot of sensitivity versus 1-Specificity which indicates how effectively the test identifies the diseased and non-diseased people. The general structure of a ROC curve is shown in Figure 2-15. There is a diagonal line joining (0, 0) and (1, 1) which represents a random chance to distinguish people with versus those without a disease. If the performance of a diagnostic test is no better than chance level the ROC curve lies on the diagonal line. If a diagnostic test perfectly distinguishes between the diseased and non-diseased people (100% sensitivity and 100% specificity) the ROC curve reaches the upper left corner. Each data point on the graph represents a different cut-off point with corresponding Sensitivity and Specificity.

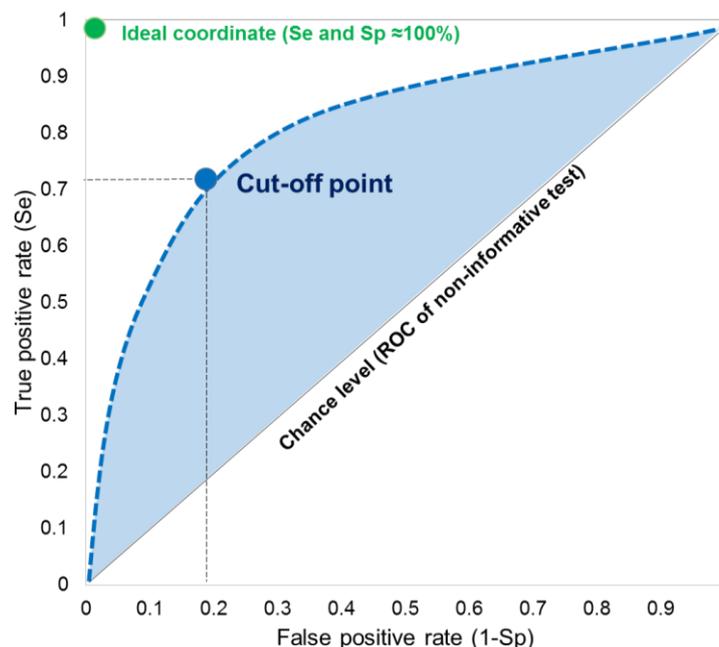


Figure 2-15. A general structure of the ROC curve

The values predicted from the model are presented as the blue dashed curve. The blue shaded area is Area under the Curve. The blue circle indicates the cut-off point with corresponding Sensitivity and Specificity (black dash lines). The green circle is the ideal point of maximum Sensitivity and Specificity. The 45° diagonal line shows the ROC of an uninformative test.

- *Area Under the Curve (AUC)* is a quantitative summary measure of the ROC curve. Its values range from 0 to 1 where a perfect diagnostic test will have an AUC value of 1, whereas a worthless diagnostic test will have an AUC ≤ 0.5 . “ROC PLOT” macros was used to plot ROC curves and calculate associated statistics (<http://support.sas.com/kb/25/018.html>).

An ideal diagnostic test that has perfect sensitivity and perfect specificity can determine disease status with certainty (i.e., no misclassification) (Figure 2-16, left image). However, in the real world almost all tests to some extent miss disease or indicate disease in normal people (Figure 2-16, image B, C, D). The relative importance of a false negative versus a false positive diagnosis varies according to the diagnostic tests and disease of interest (Mallett et al., 2012). Therefore, for many diagnostic tests, there are multiple potential thresholds. For example, if the diagnostic test is used for screening a life threatening disease, a more sensitive but less specific cut-off is preferable because missing a case is regarded as much more important than making a false positive diagnosis in a healthy person (Mallett et al., 2012). However, a more specific but less sensitive threshold is preferable when a diagnostic test is used to select people who represent a particular subgroup (“phenotype”) which is different from the general population.

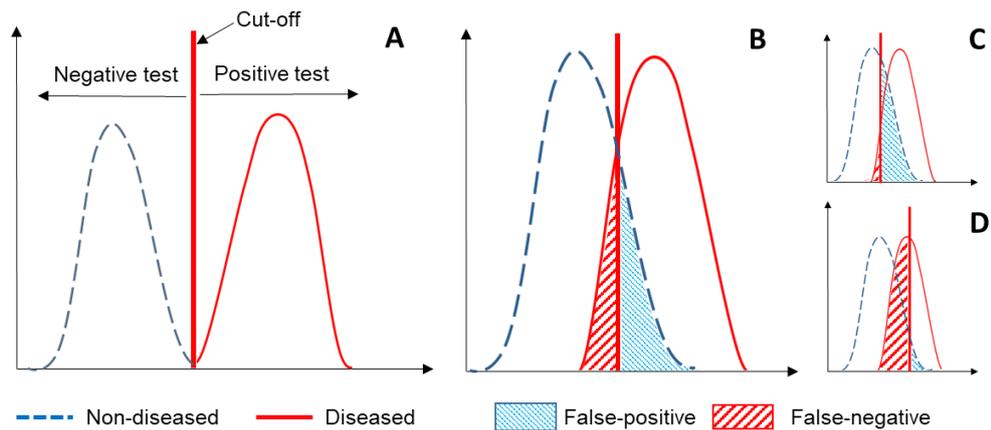


Figure 2-16. Different decision thresholds.

A cut-off value is represented by the vertical red line. All test values equal or greater than this value are considered positive, otherwise they are considered negative.

A. A diagnostic test with perfect sensitivity and perfect specificity.

B, C, D. The distribution curves overlap meaning that the diagnostic test cannot fully separate diseased and non-diseased people. If the test indicates disease in normal people, these people are false-positives (over-diagnosed). Those people with disease classified by the test as negative are false-negatives (missed cases). The cut-off "B" is corresponding with maximum sensitivity and specificity. As the cut-off value decreases (C), the test Sensitivity increases and the test Specificity decreases. Increasing the cut-off value (D) will give you a more specific but less sensitive test.

Three **cut-offs** were identified and examined in this study:

- Youden index: A threshold with the maximum sensitivity and specificity ($J = \text{Maximum} (\text{Sensitivity} + \text{Specificity} - 1)$) (Habibzadeh et al., 2016). The results range between 0 to 1, where J=1 indicates that there is no false-negative or false-positive values, and J=0 indicates that the diagnostic test cannot differentiate between diseased and non-diseased subjects.
- A threshold with a relatively high specificity of 90% to ensure the minimum misdiagnosis.
- A threshold of 4 mm recommended by EULAR (D'Agostino et al., 2005).

2.7.5. Case-control study with both cross-sectional and follow-up data

Cross-sectional study. At baseline the association between US features and knee pain was estimated using multinomial logistic regression (“proc LOGISTIC”, SAS). This is an extension of binary logit regression when the categorical dependent variables have more than two response categories. The “No knee pain” group was chosen as a reference (base) group. The OR and 95% CI were used as the measure of association. All models were adjusted for potential confounding factors such as age, gender, BMI and also for radiographic changes, and were checked for interactions and collinearity. Because cases and controls were not fully matched, unconditional regression analysis was chosen. Missing values constituted less than 10%.

Cohort study. At one year follow-up two analyses were performed:

1. *The association between changes in pain and changes in US values* was examined in people with early knee pain assessed at baseline and at one year. Absolute changes in effusion, synovial thickness and pain NRS scores were calculated by subtracting the baseline measure from the follow-up measure within individuals. Then a correlation analysis was undertaken.
2. *Potential baseline predictors for KP worsening* as defined by PGA were examined using multivariate logistic regression analysis. The analysis was carried for all participants from the “Early knee pain” and “Established knee pain” groups who completed the follow-up questionnaire. Sensitivity analysis was undertaken using an

alternative definition of knee pain worsening, defined by the meaningful increase from baseline in pain severity on NRS. The least significant criterion (LSC) was used to calculate the meaningful change taking into account measurement error and the correlation between the baseline and follow-up measurements (Nguyen and Eisman, 2000, Wang et al., 2016b). The equation was: $LSC = 1.96 \times \sigma \sqrt{2(1 - \rho)}$, where σ is the standard error of the mean difference between baseline and follow-up; and ρ is the serial correlation. In this study the LSC was calculated to be ± 1 on NRS (scale 0-10).

Additional analysis. *At baseline* the association of synovial changes detected on US with radiographic severity was examined using a two-level generalised linear mixed model to adjust for cluster effects (i.e., the difference between the three groups). *At one year follow-up* the association between baseline radiographic score and increase in effusion or synovial hypertrophy was examined using a linear regression analysis with adjustment for age, gender and BMI.

2.7.6. Contribution of central versus peripheral risk factors (including US) to knee pain

The focus of this cross-sectional study was to determine the association between multiple risk factors, including synovial changes detected on US, and knee pain, and the role of synovitis in different types of knee pain. A three-step analysis was undertaken.

Firstly, ORs between multiple risk factors (sub-grouped as central, peripheral and other) and knee pain using multivariate logistic regression were calculated. OR for each risk factor was adjusted for age, gender and BMI to allow the comparison between them. Based on the logistic regression model ROC analysis was undertaken with knee pain as an outcome (Sullivan et al., 1995, Hanley and McNeil, 1982, Pencina et al., 2008). **The proportional risk contribution (PRC)** for the risk factors combined within sub-groups was examined by the ROC difference between the full risk factor model (AUC_{full}) and the partial model without an exposure of interest ($AUC_{partial}$): $PRC = \frac{AUC_{full} - AUC_{partial}}{AUC_{full} - 0.5}$, where 0.5 is the AUC under the diagonal line of the ROC curve that reflects no discrimination/prediction of the specific risk factor for the disease of interest. For example, if AUC for the full model is equal 0.9 and AUC for partial model is equal 0.75, the contribution from the exposures of interest is 37.5%.

Secondly, we examined the association between synovial changes detected on US and knee pain in four subgroups (ROA present/absent and WSP present/absent). Pain-free participants without ROA and WSP

were chosen as a reference (control) group. ORs were adjusted for age, gender and BMI.

Thirdly, we conducted ***within-person analysis*** in participants with unilateral knee pain to further refine the association between knee pain and the US synovial features. A one person two knees (painful knee versus pain-free knee) comparison is a unique case control study where two knees within each individual form a matched set, hence the influence from central pain mechanisms is fully balanced (Neogi et al., 2009). As the matched knees were nested within individuals, which were further nested within two groups (participants from case-control and cross-sectional study), a multilevel generalized linear mixed modelling was applied to adjust for the cluster effects (i.e., the difference between groups) (“proc GLIMMIX”, SAS). In addition, we sub-grouped them by the presence/absence of ROA to confirm findings from our analysis of four subgroups (ROA present/absent and WSP present/absent).

All statistical analyses were undertaken in SAS software v9.4 licenced to the University of Nottingham.

3. RESULTS

This chapter provides the results of all studies undertaken for this Ph.D.

The first section of this chapter (3.1) presents and discusses the results of a systematic review and meta-analysis of observational studies on “Synovial changes detected by ultrasound in people with knee OA”. This study provides a summary of all available previous studies that report the prevalence of synovial changes in people with knee pain/OA, and also in the general population. As a secondary objective, studies reporting the association between US features and knee pain and radiographic changes are also summarised. This systematic literature review summarises the current evidence about the topic and identifies current gaps in our knowledge which will be addressed in the following sections.

The second section of this chapter (3.2) reports the intra and inter-observer reliability of the US and radiographic measures undertaken in the thesis.

The third section (3.3) provides an overview of the cross-sectional study undertaken on a sample of the general population. Findings from this study include the normal ranges of synovial changes detected on US, distribution by age, gender and laterality, and the optimal threshold for both effusion and synovial hypertrophy.

Section 3.4 aimed to examine whether synovial changes detected on US associated with knee pain cross-sectionally, whether changes in effusion or hypertrophy on US correlated with changes in knee pain over one year,

and whether synovial changes detected on US at baseline predicted knee pain worsening at follow-up.

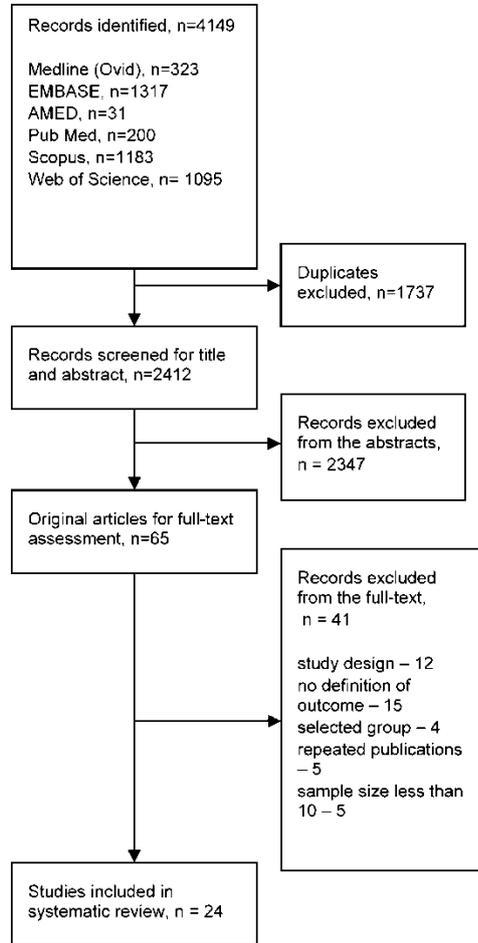
Section 3.5 reports the results of the cross-sectional study with the aim of exploring the contributions of all collected risk factors including central, peripheral and other factors to knee pain, and the role of synovitis in different types of knee pain.

3.1. Systematic review of literature on ultrasound synovial changes

3.1.1. Selection of studies

The first search yielded 4,149 titles and abstracts, of which 65 potentially relevant publications were considered for full-text assessment. Forty-one studies were excluded by reading full-text papers, leaving a total of 24 studies which met the inclusion criteria. The second search returned 4479 citations of which only 3 met inclusion criteria and two additional studies were identified from the reference search (Figure 3-1). All studies were published between 1990 and 2015. Three studies were translated from German, Italian and Russian (Martino et al., 1992, Mielke et al., 1990, Svetlova and Vezikova, 2010) but all other studies were written in English.

1. Studies in people with knee pain or knee OA



2. Studies in the general population

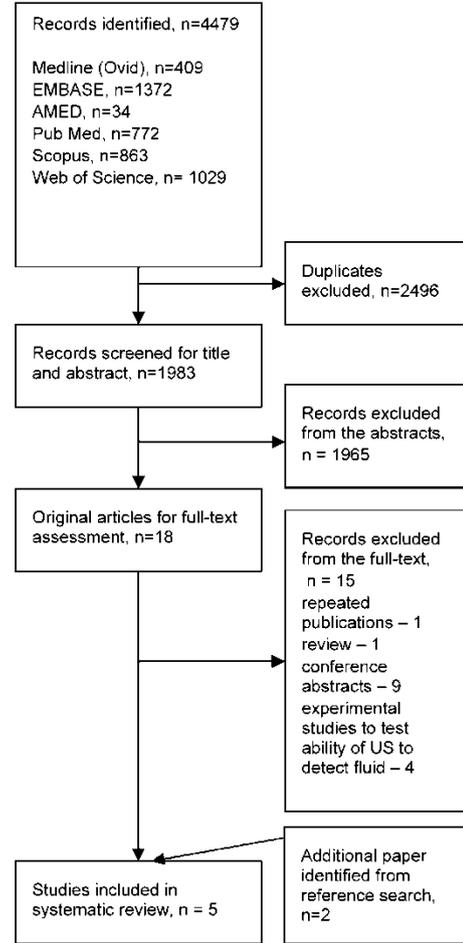


Figure 3-1. Study selections

3.1.2. Characteristics of studies

Data for prevalence were derived from both cross-sectional and case-control studies. Of 24 studies reporting the prevalence of US-detected effusion, synovial hypertrophy and DS in people with knee pain/OA, 14 were case-control and 10 were cross-sectional in design. Only four studies were community-based, the rest recruited participants from hospital populations except for four studies which did not declare the setting (Blankstein et al., 2006, Malas et al., 2014, Zivanovic et al., 2009b, Tarhan and Unlu, 2003). The sample size ranged from 10 to 600 with nine studies reporting a sample size of more than 100. Age varied from 36 to 74 years. There were 20 studies of people with symptomatic knee OA (defined by ACR criteria) and 4 studies of people with knee pain irrespective of any underlying structural change. Three studies comprised more than one study group (de Miguel Mendieta et al., 2006, Wu et al., 2012, Hall et al., 2014).

Four cross-sectional studies and one case-control study (in comparison with RA) explored prevalence and characteristics of US features in the general population (Abraham et al., 2014, D'Agostino et al., 2015) and in pain-free volunteers (Schmidt et al., 2004, Martino et al., 1992, Mielke et al., 1990). None of these five studies obtained radiographic data. Three of the five studies (range 50 to 488) recruited more than 100 subjects (D'Agostino et al., 2015, Abraham et al., 2014, Schmidt et al., 2004). Age range was from 37 to 73 years.

Ten of the 29 studies were funded from academic sources, one declared no funding, one had commercial support and the others did not specify funding sources. Baseline demographic characteristics (age, gender, BMI, pain assessment and radiographic score) were generally well reported. Table 3-1 summarises the main characteristics of included studies. More details are in Appendix 8.

Definitions of US pathology varied from dichotomous measures (with different thresholds) to individual scoring systems (0-3 or 0-4 scale) or summative quantitative systems (adding effusion, synovial thickness and/or DS). Appendix 9 provides an overview of US scoring systems used in these studies.

Table 3-1. Characteristics of the included studies

	People with knee OA/pain*	General/normal population
Number of studies	24	5
Number of participants	3713	1007
Mean age (years)	61.05	52.74
Women (%)	75.03	48.93
Mean BMI** (kg/ m2)	28.2	25.33

Note: * including control groups; ** BMI – body mass index.

3.1.3. Study quality assessment

Of 24 studies in people with knee OA/pain 12 had a score of $\geq 50\%$. In cross-sectional studies the NOS quality scores ranged from 2 to 9 stars with a median score of 5.5 (maximum 10). Three studies scored less than 5 (Picerno et al., 2013, Artul et al., 2014, Malas et al., 2014). In general, all samples were selected non-randomly, provided adequate definition of cases (ACR-criteria for OA diagnosis or a validated tool for knee pain assessment) and utilised “blinded” US assessments. The scores on each of the seven criteria and total scores for each study are presented in Table 3-2.

The quality of the case-control studies varied from 1 to 6 stars with a median score of 4 (maximum 9) (Table 3-3). Overall the majority of studies had an adequate case definition (ACR criteria or ROA). The definition of controls included no history of joint disease and no OA as defined.

Table 3-2. Quality assessment of cross-sectional studies using the Newcastle-Ottava Scale

Author, year	Selection				Comparability	Outcome		Total stars	Standardised quality score (% of the maximum score)
	1	2	3	4		5	6		
Bevers, 2014	★			★★		★★		5	50
Chan, 2014	★			★★		★★	★	6	60
D'Agostino, 2005	★	★		★★	★★	★★	★	9	90
Kumm, 2009	★			★	★★	★★		6	60
Mendieta, 2006				★★	★★	★★	★	7	70
Picerno, 2013	★					★★		3	30
Ulasli, 2014	★			★★		★★	★	6	60
Arthul, 2014						★★		2	20
Iagnocco, 2010	★			★★		★★		5	50
Malas, 2014				★★		★	★	4	40
Maximum number of stars per question (10)	1	1	1	2	2	2	1		

Table 3-3. Quality assessment of case-control studies using the Newcastle-Ottava Scale

Author, year	Selection				Comparability	Exposure			Total stars	Standardised quality score (% of the maximum score)
	1	2	3	4		5	6	7		
Beitinger, 2013	★			★		★	★		4	44.44
Chatzopoloulos, 2008	★		-	-	-	★	-		2	22.22
Hall, 2014	★			★ ★		★	★		5	55.56
Jung, 2006	★	★	-	-	-		-		2	22.22
Naredo, 2005	★	★		★		★	★		5	55.56
Song, 2008	★					★			2	22.22
Tarhan, 2003	★			★		★	★		4	44.44
Tchetina, 2013	★			★ ★	★	★			5	55.56
Walther, 2001	★			★		★	★		4	44.44
Wu, 2012	★			★	★★	★	★		6	66.67
Zivanovic, 2009	★		-	-	-		-		1	11.11
Kristoffersen, 2006	★	★				★	★		4	44.44
Blankstein, 2006				★	★★		★		4	44.44
Svetlova, 2010	★			★	★★		★		6	66.67
Maximum number of stars per question (9)	1	1	1	1	2	1	1	1		

3.1.4. Prevalence of ultrasound features in people with knee osteoarthritis/pain

Of the 24 included studies, 21 had data for effusion, 13 for hypertrophy and 7 for DS. The pooled prevalence was 51.5%, 41.5% and 32.7%, respectively. Studies were highly heterogeneous but only studies involved in the meta-analysis for hypertrophy had significant publication bias (Table 3-4). Funnel plots are resented in Appendix 11.

Several subgroup analyses were undertaken according to US threshold for abnormality, sample size of study, overall quality of study and definition of OA. The results are summarised in Table 3-5. In general, larger studies (≥ 100) tended to give a lower prevalence than smaller studies (< 100). Similarly, higher quality studies (overall score $\geq 50\%$) tended to have a lower prevalence than lower quality studies (overall score $< 50\%$). This was especially true when DS was assessed, where a clear separation was observed between higher and lower quality studies (Figure 3-2). Interestingly, people with either ACR or ROA had greater prevalence of all three US abnormalities than people with knee pain alone (Table 3-5).

3.1.5. Prevalence of ultrasound features in the general/normal population

Among 5 studies identified from the second search, two provided data on prevalence of US detected synovial effusion in the general population (Abraham et al., 2014, D'Agostino et al., 2015). In addition, four normal

(i.e. asymptomatic) control groups from the case control studies (Blankstein et al., 2006, Naredo et al., 2005, Tarhan and Unlu, 2003, Hall et al., 2014) reported prevalence of US synovial effusion. These made a total number of 6 studies in this analysis (Table 3-4). The pooled prevalence of US synovial effusion was 19.9% (95%CI 7.8% to 35.3%), approximately 2-3 times lower than that in people with knee OA/pain (51.5%, 95%CI 40.2% to 62.8%, Table 3-4). Similarly, four studies (Blankstein et al., 2006, D'Agostino et al., 2015, Tarhan and Unlu, 2003, Hall et al., 2014) provided data for hypertrophy and two studies (D'Agostino et al., 2015, Hall et al., 2014) for DS. The prevalence of these findings was much lower in the general/normal population than in people with knee OA/pain. The studies were highly heterogeneous but had no evidence of publication bias (Table 3-4).

Table 3-4. Prevalence of ultrasound-detected findings in people with knee osteoarthritis/pain

	Number of studies	Number of subjects	Pooled prevalence (95% CI)	I ² % (P _{heter})	P _{pub}
People with knee OA/pain					
Effusion	21	3266	51.5 (40.2 to 62.8)	97.5 (<0.0001)	0.082*
Synovial hypertrophy	13	1785	41.5 (26.3 to 57.5)	97.6 (<0.0001)	0.026*
Doppler Signal	7	538	32.7 (8.34 to 63.24)	98.0 (<0.0001)	0.493*
The general/normal population					
Effusion	6	922	19.9 (7.81 to 35.34)	94.7 (<0.0001)	0.587*
Synovial hypertrophy	4	601	14.5 (0 to 58.81)	98.7 (<0.0001)	0.118**
Doppler Signal	2	533	15.8 (3.08 to 35.36)	93.8 (<0.001)	-

Note: * Egger's test ** Harbord's test.

CI - confidence interval; I² - inconsistency; P_{heter} - p-value for heterogeneity; P_{pub} - p-value for publication bias.

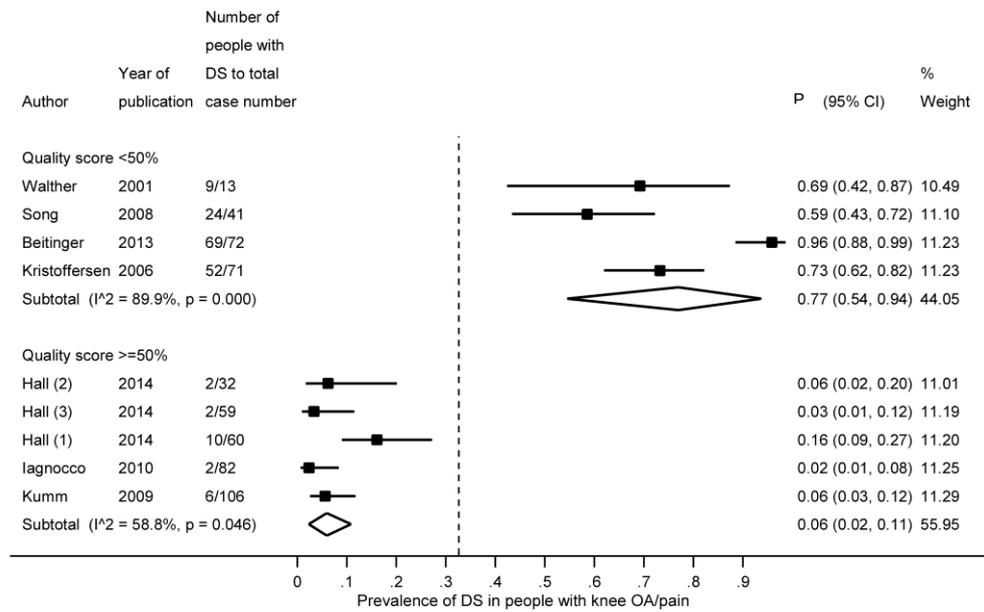


Figure 3-2. Forest plot showing the subgroup analysis by overall quality score for the prevalence of Doppler Signal (DS) in people with knee osteoarthritis/pain

Note: P- prevalence rates, 95% CI – lower and upper confidence limits of the 95% confidence interval around the mean prevalence rate.

The diamond in the forest plot denotes the summary prevalence and its edges the respective 95% CI.

Three groups from the study by Hall were included: (1) – people with symptomatic osteoarthritis (OA), (2) – people with radiographic OA, (3) – people with knee pain

Table 3-5. Subgroup analysis in studies on people with knee osteoarthritis/pain

Subgroup analysis	Effusion			Synovial hypertrophy			Doppler signal		
	Number of studies	Prevalence (95% CI)	P*	Number of studies	Prevalence (95% CI)	P*	Number of studies	Prevalence (95% CI)	P*
Threshold:									
≥ 4 mm	11	52.5 (38 to 66.8)		10	43.1 (26.5 to 60.5)				
≥ 2 mm	7	67.6 (55.8 to 78.3)		2	25.5 (14.5 to 38.2)				
Absent or present	6	32.7 (13.9 to 54.9)	0.018	3	46.9 (0 to 99.7)	0.234			
Sample size:									
≥ 100 subjects	9	37.1 (20.8 to 55.2)		5	21.4 (12.4 to 32.1)		1		
< 100 subjects	15	60.8 (48.4 to 72.5)	0.034	10	52.8 (29.3 to 75.7)	0.015	8		
Quality score:									
< 50%	10	54.7 (32.1 to 76.4)		5	47.1 (8.4 to 88.0)		4	77 (54.5 to 93.7)	
≥ 50%	14	49.2 (37.3 to 61.2)	0.677	10	38.5 (24.7 to 53.4)	0.726	5	6.0 (2.4 to 10.9)	<0.0001
Case definition:									
Knee OA	14	58.7 (47 to 69.9)		12	49 (30.5 to 67.6)		7	43.8 (11.7 to 79.0)	
Knee pain	5	26 (5.6 to 54.4)	0.037	3	15.2 (3.3 to 33.3)	0.010	2	4.8 (1.9 to 8.7)	0.009
Study design:									
Cross-sectional	11	43.0 (28.0 to 58.0)		5	25.0 (17.0 to 34.0)		2	4.0 (2.0 to 8.0)	
Case-control	13	59.0 (41.0-76.0)	0.180	10	50.0 (24.0 to 76.0)	0.07	7	44.0 (13.0 to 78.0)	<0.0001
Doppler signals:									
Colour Doppler							2	87.0 (80.0 to 92.0)	
Power Doppler							7	20.0 (4.0 to 42.0)	
Not stated							1	6.0 (3.0 to 12.0)	<0.0001
Mean age:									
≤60	9	53.0 (42.0 to 63.0)		5	24.0 (13.0 to 38.0)		1		
> 60	13	61.0 (47.0 to 74.0)	0.070	9	55.0 (28.0 to 80.0)	0.050	7		
Women proportion:									
≤70	8	51.0 (29.0 to 73.0)		7	31.0 (16.0 to 49.0)		7		
> 70	14	59.0 (48.0 to 70.0)	0.520	7	58.0 (30.0 to 84.0)	0.110	1		

Note: * p-value for testing heterogeneity between subgroups. CI - confidence interval; OA – osteoarthritis.

3.1.6. Associations of ultrasound-detected synovial changes with pain and structural changes

Ten studies examined the relationship between knee pain and synovial changes detected on US. Overall, most studies reported a positive association between knee effusion and pain (7 of 10 studies) but no association between synovial hypertrophy and pain (4 of 6) and there were no data for DS (Table 3-6).

Table 3-6. Associations between effusion and synovial hypertrophy with pain

Author, year	Sample size	Mean age (SD/range)	Proportion of women	Standardised quality score (% of the maximum score)	Association between effusion and pain	Association between synovial hypertrophy and pain
Bevers 2014*	180	57 (9.2)	66.7	50	no association	no association
Song 2008	41	65 (6.7)	63.4	22.2	no association	no association
Ulasli 2014	86	56.2 (10.2)	80.2	60.0	no association	
Hall 2014	62	73.9 (7.8)	67.7	55.6	positive association	positive association
D'Agostino 2005*	600	66.7 (9.8)	72.5	90.0	positive association	no association
Malas 2014	61	58.88 (7.2)	83.6	40.0	positive association	
Mendieta 2006	101	62.1 (9)	70.0	70.0	positive association with pain on motion	
Chan 2014	193	59 (13.9)	74.1	60.0	positive association with pain on walking, but not while sitting	positive association with pain while sitting, but not walking
Wu 2012*	56	62.9 (8.2)	75.0	66.7	positive association with pain during movement, but not at rest	no association with pain on movement and at rest
Naredo 2005	50	64.3 (7.9)	88.0	55.6	positive association with pain during movement and at rest	
% positivity					7/10	2/6

Note: * adjusted for radiographic severity. SD – standard deviation.

Three studies examined knee pain on walking and at rest separately (Chan et al., 2014, Wu et al., 2012, Naredo et al., 2005). Two studies did not find any association between knee effusion and pain at rest (Chan et al., 2014, Wu et al., 2012), whereas this association was observed by Naredo et al. (2005). Both studies examined synovial hypertrophy but found no association with pain on walking and indefinite results with pain at rest (Chan et al., 2014, Wu et al., 2012). Unfortunately, these studies did not provide sufficient data for statistical pooling so the strength of the association between knee pain and US effusion/synovial hypertrophy remains unknown.

Only two studies examined the relationship between Doppler activity and pain, both of them recruiting people with symptomatic knee OA with disease duration more than 6 months. Song et al. (2009) found a positive correlation ($r=0.366$; $p=0.020$) between DS and knee pain in people with moderate to severe knee pain (mean pain score - 68.3 (SD 19.6)) and structural changes on radiographs ($K\&L\geq 2$). The study by Iagnocco et al. (2010) revealed a significant association between total US score (effusion, synovial hypertrophy and DS score in both knees) and pain ($p=0.004$) in participants with knee pain more than 20 mm on a 100mm VAS (mean pain score 48.4 mm (SD 19.9)).

Three studies examined the association between US-detected abnormalities and radiographic severity (D'Agostino et al., 2005, Wu et al., 2012, Hall et al., 2014). A positive association was observed in two studies which directly addressed the association between synovial

changes and radiographic severity (D'Agostino et al., 2005, Hall et al., 2014). For example, knee effusion or abnormal synovial thickness on US were associated with radiographic OA, defined as K&L \geq 3 in one study with ORs of 1.91 (95% CI 1.32 to 2.77) and 2.2 (95% CI 1.33 to 3.64), respectively (D'Agostino et al., 2005). This association was independent of pain, whereas the association between US features and pain was highly dependent on the severity of radiographic changes and only significant in people without OA (K&L \leq 2). These findings were supported by a recent study by Hall et al. (2014) in which four groups were compared (asymptomatic normal control, knee pain only, radiographic knee OA (K&L \geq 2) only, and knee pain plus ROA). This study found no difference between the normal control and knee pain groups, but significantly higher scores in both the asymptomatic ROA and symptomatic ROA groups. The prevalence was 29%, 32%, 81%, and 92% for effusion (\geq 4mm); 8%, 12%, 41% and 82% for hypertrophy (\geq 4mm); and 2%, 3%, 6% and 16% for DS (any grade), respectively. In addition, this study followed participants for 3 months and found no association between change in pain and change in US features. The study of Wu et al. (2012) did not explore directly the association between US findings and structural changes. Participants with knee OA who had bilateral equal K&L scores showed significant differences between symptomatic and asymptomatic knees ($p=0.016$ for effusion and $p<0.001$ for synovial hypertrophy), suggesting that synovial changes are related more to pain than structural severity. However, this single study does not allow a strong conclusion to be drawn.

3.1.7. Summary

This systematic literature review highlighted that although a number of predominantly hospital-based studies have been undertaken in knee OA to examine synovial changes detected on US, the normal values, the threshold for abnormality, and the frequencies of these features in the general population and in community-based people with KP or OA are largely unknown.

3.2. Reproducibility

3.2.1. US assessment

Twelve participants (24 knees) and four volunteers (8 knees) took part in the reliability assessment and had both knees scanned independently by two examiners (MH and AS) on the same day. There were 7 women and 9 men, with a mean age of 62.75 years (SD 2.47, range 42-80). Four volunteers, mean age 60.75 years (SD 2.69, range 54-66), 2 women and 2 men, were later reassessed by the same examiner (AS) within a 7 day period.

The inter-observer agreement for dichotomous variables was moderate for effusion and substantial for synovial hypertrophy (kappa 0.44 and 0.61, respectively). The agreement on the continuous measures was good for effusion and moderate for synovial hypertrophy (concordance correlation coefficient 0.75 and 0.70, respectively, both $p < 0.0001$). The mean difference between observers was less than 0.5 mm for both continuous measures.

The intra-observer agreement in detecting effusion was moderate for dichotomous (kappa 0.50) and excellent for continuous values (0.950, $p < 0.0001$). Because sample size was small ($n=8$) and there were no positive results for synovial hypertrophy, kappa statistics were not calculated. However, the agreement on continuous measures of synovial thickness was good (concordance correlation coefficient 0.843, $p < 0.0001$).

Table 3-7 lists the mean k values, overall agreement, Lin's concordance correlation coefficient with 95% confidence intervals, and mean difference between two measurements with SD and 95% limits of agreement for inter- and intra-observer reliability. All data presented are for effusion and synovial hypertrophy. The agreement on positive DS could not be calculated because the prevalence of this finding was very low.

Bland and Altman plots both for effusion and synovial thickness measures showed no tendency for the magnitude of the difference to be dependent on the magnitude of the individual measures (Figure 3-3, Figure 3-4, respectively). In addition, the observed average agreement did not deviate much from the line of perfect agreement equal to 0 (mean difference <0.03 mm for effusion and <0.40 mm for synovial hypertrophy). This means that there is no consistent bias between observers.

Table 3-7. Intra- and Inter-observer agreement for ultrasound features

	Kappa*, (95% CI)	Agreement, %	Concordance coefficient (95% CI)**	Mean difference in mm (SD; 95% limits of agreement)
Effusion				
<i>Inter-observer</i>	0.44 (0.14 to 0.75)	71.88	0.75 (0.60 to 0.90)	-0.01 (1.79; -3.52 to 3.50)
<i>Intra-observer</i>	0.50 (0.02 to 1)	75	0.95 (0.89 to 1.01)	-0.03 (0.76; -1.51 to 1.46)
Synovial hypertrophy				
<i>Inter-observer</i>	0.61 (0.22 to 1)	90.63	0.70 (0.52 to 0.88)	-0.40 (1.85; -4.02 to 3.21)
<i>Intra-observer</i>	n/a	n/a	0.84 (0.65 to 1.03)	0.31 (0.70; -1.06 to 1.68)

Note: * unweighted Cohen's kappa ** Lin's concordance correlation coefficient using the asymptotic point estimate and variance, n/a – estimate is not available.

SD – standard deviation; CI - confidence interval.

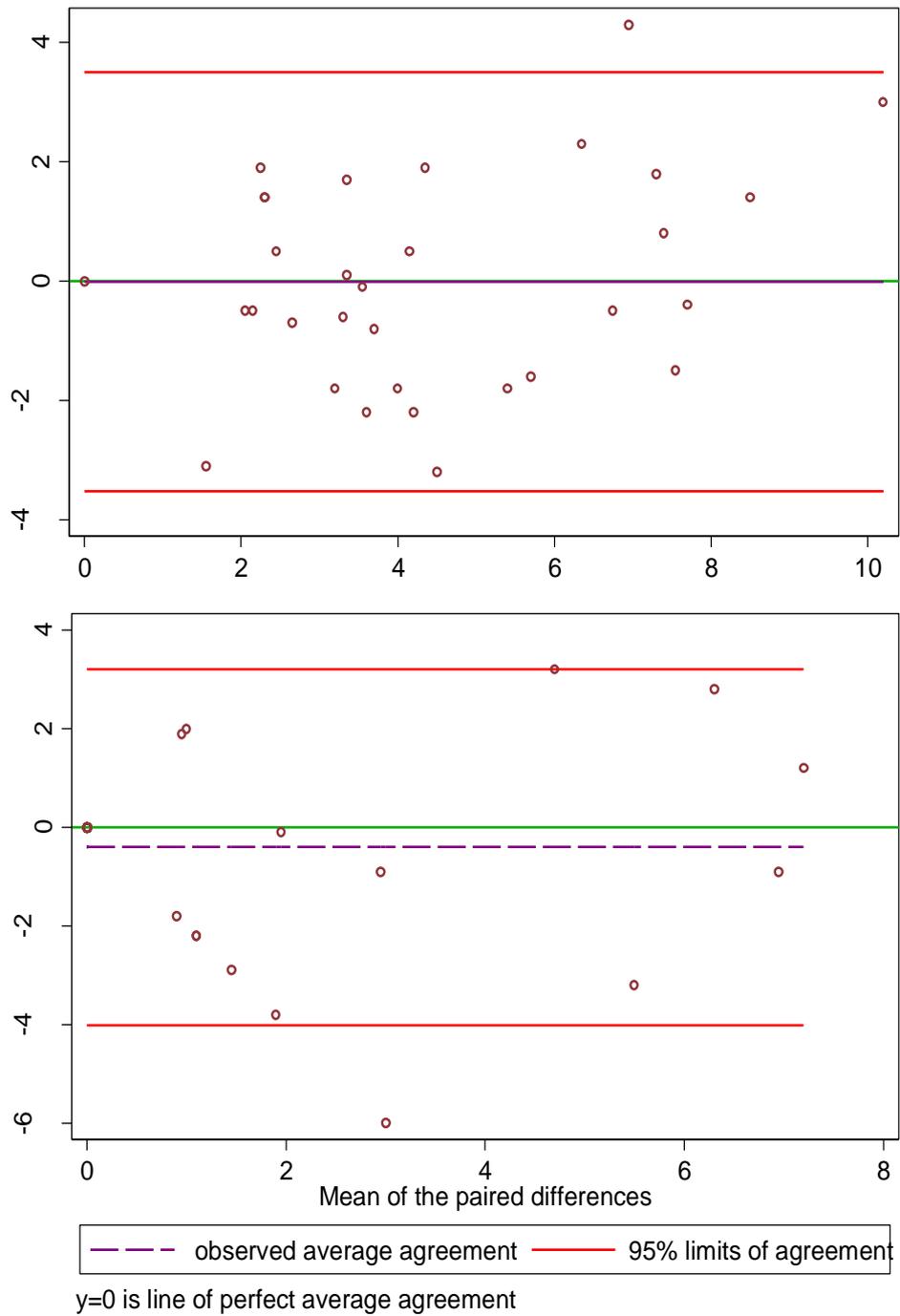


Figure 3-3. Bland and Altman plots for inter-observer agreement of ultrasound measure of effusion and synovial hypertrophy

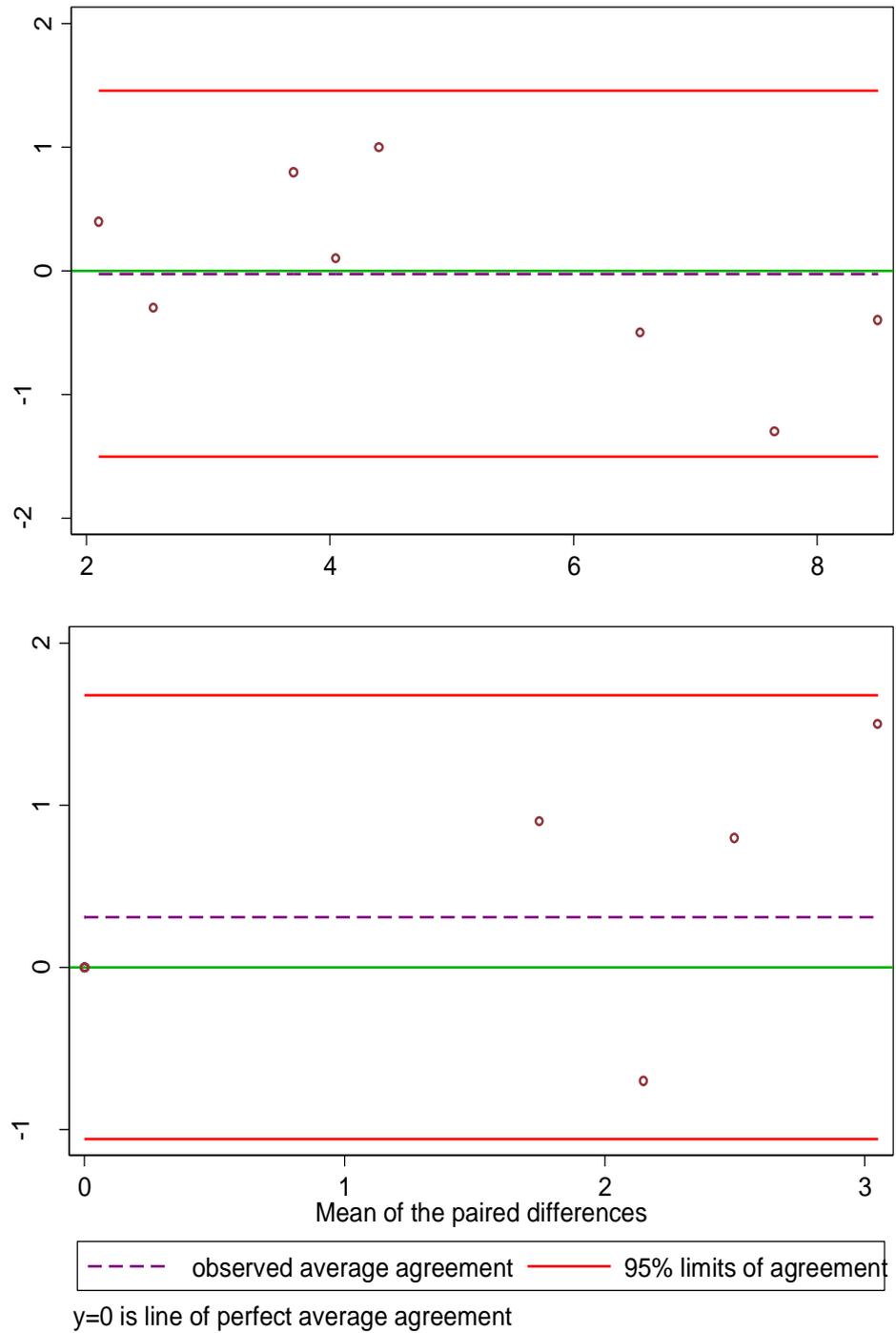


Figure 3-4. Bland and Altman plots for intra-observer agreement of ultrasound measure of effusion and synovial hypertrophy

3.2.2. Scoring of radiographs

3.2.2.1. Inter-observer agreement during the training period

The raters demonstrated a substantial agreement for osteophytes and JSN grading (kappa 0.60 and 0.80, respectively) and excellent agreement for K&L scoring (kappa 0.84) in the TFJ. The level of agreement was moderate for all three categories in the PFJ (kappa 0.57, 0.51 and 0.52, respectively) (Table 3-8). Inter-rater agreement on continuous measures was almost perfect (concordance correlation coefficient 0.90-0.97) (Table 3-8). Mean difference in JSW between observers was 0.03 mm (SD 0.62; 95% limits of agreement -1.18 to 1.24) for the TFJ and 0.08 mm (SD 1.01; 95% limits of agreement -2.06 to 1.89) for the PFJ. Overall results of agreement testing showed that the trainee achieved satisfactory scoring skills.

Table 3-8. Inter-observer agreement for radiographic OA features during the training period

	Kappa-statistics* (95% CI)
Osteophytes (TFJ)	0.60 (0.50 to 0.70)
Osteophytes (PFJ)	0.57 (0.50 to 0.65)
Osteophytes (whole knee score)	0.59 (0.53 to 0.65)
Joint space narrowing (TFJ)	0.80 (0.70 to 0.87)
Joint space narrowing (PFJ)	0.51 (0.37 to 0.64)
Joint space narrowing (whole knee score)	0.69 (0.60 to 0.77)
ROA ¹	0.86 (0.70 to 1.00)
K&L score (TFJ)	0.84 (0.72 to 0.93)
K&L score (PFJ)	0.52 (0.37 to 0.68)
K&L score (whole knee score)	0.69 (0.59 to 0.79)
	Concordance correlation coefficient (95% CI)
Joint space width (TFJ)	0.97 (0.95 to 0.98)
Joint space width (PFJ)	0.90 (0.86 to 0.94)

Note: * weighted Cohen's kappa.

Agreement calculated for two observers (SD and AS).

CI - confidence interval; TFJ – tibio-femoral joint; PFJ – patello-femoral joint;

¹radiographic OA defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

3.2.2.2. Inter-observer agreement for the KPIC study

The agreement testing was performed twice between two assessors (GSF and AS) in order to identify disagreements and improve scoring technique. For the first round, images from the sample of 23 participants described earlier were scored. The agreement was substantial for all categorical data in the TFJ (kappa for osteophytes, JSN and K&L scoring 0.65, 0.71 and 0.68, respectively) and for osteophyte grading in the PFJ (kappa 0.65). However, agreement on JSN and K&L scoring was fair (kappa 0.38 and 0.58, respectively). All disagreements were discussed together with Michael Doherty (Professor of Rheumatology).

The second round of testing was performed on images from 21 participants. The agreement on all three categories in both knee compartments reached a substantial level (kappa from 0.64 to 0.78), which was acceptable as a satisfactory result. Agreement on continuous measures was excellent (>0.9 for JSW in both TFJ and PFJ).

The third round of testing was performed on images from 20 participants. The agreement on all three categories in both knee compartments slightly increased with kappa ranging from 0.65 to 0.83). Results are summarised in Table 3-9.

Table 3-9. Inter-observer agreement for radiographic OA features

	Kappa-statistics* (95% CI)		
	After training	Before scoring for the study	During scoring for the study
Osteophytes (TFJ)	0.65 (0.56; 0.75)	0.71 (0.63; 0.79)	0.79 (0.67; 0.87)
Osteophytes (PFJ)	0.65 (0.57; 0.73)	0.64 (0.56; 0.71)	0.78 (0.69; 0.84)
Osteophytes (whole knee score)	0.66 (0.60; 0.72)	0.68 (0.63; 0.73)	0.79 (0.72; 0.84)
Joint space narrowing (TFJ)	0.71 (0.58; 0.81)	0.66 (0.52; 0.77)	0.82 (0.72; 0.91)
Joint space narrowing (PFJ)	0.38 (0.20; 0.57)	0.72 (0.61; 0.82)	0.78 (0.53; 0.91)
Joint space narrowing (whole knee score)	0.59 (0.48; 0.69)	0.69 (0.60; 0.76)	0.83 (0.73; 0.89)
K&L score (TFJ)	0.68 (0.53; 0.80)	0.77 (0.60; 0.89)	0.66 (0.48; 0.83)
K&L score (PFJ)	0.58 (0.43; 0.77)	0.74 (0.57; 0.86)	0.76 (0.61; 0.89)
K&L score (whole knee score)	0.64 (0.53; 0.75)	0.76 (0.65; 0.84)	0.72 (0.61; 0.83)
ROA¹	0.70 (0.48; 0.92)	0.78 (0.57; 0.98)	0.65 (0.37; 0.93)
	Concordance correlation coefficient (95% CI)		
Joint space width (TFJ)	0.97 (0.96; 0.98)	0.94 (0.92; 0.97)	n/a
Joint space width (PFJ)	0.87 (0.81; 0.92)	0.92 (0.89; 0.95)	n/a

Note: * - weighted Cohen's kappa.

Agreement calculated for two observers (GSF and AS)

CI - confidence interval; TFJ – tibio-femoral joint; PFJ – patello-femoral joint; n/a – estimate is not available.

¹ radiographic OA defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

3.2.2.3. Intra-rater agreement

In the first test on the sample of 21 participants the intra-observer agreement was moderate for osteophytes in the PFJ and JSN in both compartments and substantial for osteophytes in the TFJ and K&L score in both compartments (Table 3-10). The agreement on continuous measures of JSW was perfect (concordance correlation coefficient 0.94-0.97). The second test included a sample of 23 participants from the US in the general population study.

Table 3-10. Intra-observer agreement for ROA features

	Kappa-statistics* (95% CI)	
	Before scoring for the study	During scoring for the study
Osteophytes (TFJ)	0.85 (0.76; 0.92)	0.88 (0.83; 0.93)
Osteophytes (PFJ)	0.76 (0.67; 0.82)	0.83 (0.74; 0.90)
Osteophytes (whole knee score)	0.80 (0.76; 0.85)	0.86 (0.81; 0.90)
Joint space narrowing (TFJ)	0.77 (0.65; 0.87)	0.89 (0.80; 0.95)
Joint space narrowing (PFJ)	0.80 (0.67; 0.89)	0.83 (0.68; 0.93)
Joint space narrowing (whole knee score)	0.79 (0.70; 0.85)	0.86 (0.78; 0.92)
K&L score (TFJ)	0.87 (0.73; 0.97)	0.93 (0.84; 0.98)
K&L score (PFJ)	0.84 (0.73; 0.93)	0.91 (0.82; 0.98)
K&L score (whole knee score)	0.86 (0.78; 0.92)	0.92 (0.86; 0.97)
ROA¹	1.00 (1.00; 1.00)	0.90 (0.77; 1.00)
	Concordance correlation coefficient (95% CI)	
Joint space width (TFJ)	0.97 (0.95; 0.98)	n/a
Joint space width (PFJ)	0.94 (0.91; 0.96)	n/a

Note: * weighted Cohen's kappa.

Agreement calculated for a single observer (AS day1 – day2)

CI - confidence interval; TFJ – tibio-femoral joint; PFJ – patello-femoral joint; n/a – estimate is not available.

¹ radiographic OA defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

3.2.3. Summary

The intra-rater and inter-rater reliability is an important issue for any study involving the acquisition and reading of images. The findings of the present study suggest that both the US measures and radiographic scores were consistent between raters on the same day with the level of agreement at least moderate. Intra-observer reliability was generally higher than inter-observer agreement.

3.3. Thresholds of ultrasound synovial abnormalities for knee pain/osteoarthritis – a cross sectional study in the general population

3.3.1. Demographic and clinical characteristics

A total of 299 participants (147 women, 152 men) were included in the analysis. Table 3-11 shows the demographic and clinical characteristics of the studied population by gender. There were no differences between the groups with respect to age, BMI, prevalence of knee pain and prevalence of ROA.

Table 3-11. Characteristics of the study population

	Men	Women	p-value*	
N	152	147		
Age (years), mean (SD)	66.64 (9.21)	65.29 (9.24)	0.2060	
BMI (kg/m²), mean (SD)	26.55 (4.47)	27.03 (5.45)	0.4025	
Knee pain¹, n (%)	89/152 (58.55)	87/147 (59.18)	0.9117	
Knee pain in the past 12 months, n (%)	56/152 (36.84)	60/147 (40.82)	0.4808	
Current knee pain², n (%)	43/152 (28.29)	49/147 (33.33)	0.3448	
Current knee pain severity (NRS 0-10), mean (SD)	1.64 (2.56)	2.13 (2.93)	0.1237	
ROA³, n (%)	41/150 (27.33)	53/143 (37.06)	0.0745	
Global radiographic score(0-60)⁴, mean (SD)				
	<i>Right</i>	5.32 (7.27)	6.10 (7.30)	0.3572
	<i>Left</i>	4.63 (6.21)	5.30 (7.59)	0.4039

Note: * P-values: t test for continuous and chi-square for categorical unless otherwise specified.

SD - standard deviation; NRS – numerical rating scale 0-10; BMI - body mass index.

¹ Pain in or around a knee on most days for at least a month.

² Knee pain on most days of the past month.

³ Radiographic OA defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

⁴ Summated score for osteophytes and joint space narrowing (NLDLDA scoring system) in tibiofemoral and patellofemoral joints (medial and lateral compartments).

3.3.2. Distribution of effusion and synovial hypertrophy

The histograms of effusion and synovial hypertrophy in the whole population with a superimposed normal curve in men and women are shown in Figure 3-5. The distribution was not Gaussian (normal) in both samples. Because of the high number of zero-values the transformation attempts were unsuccessful (Appendix 10). Therefore, we used original data for further analysis.

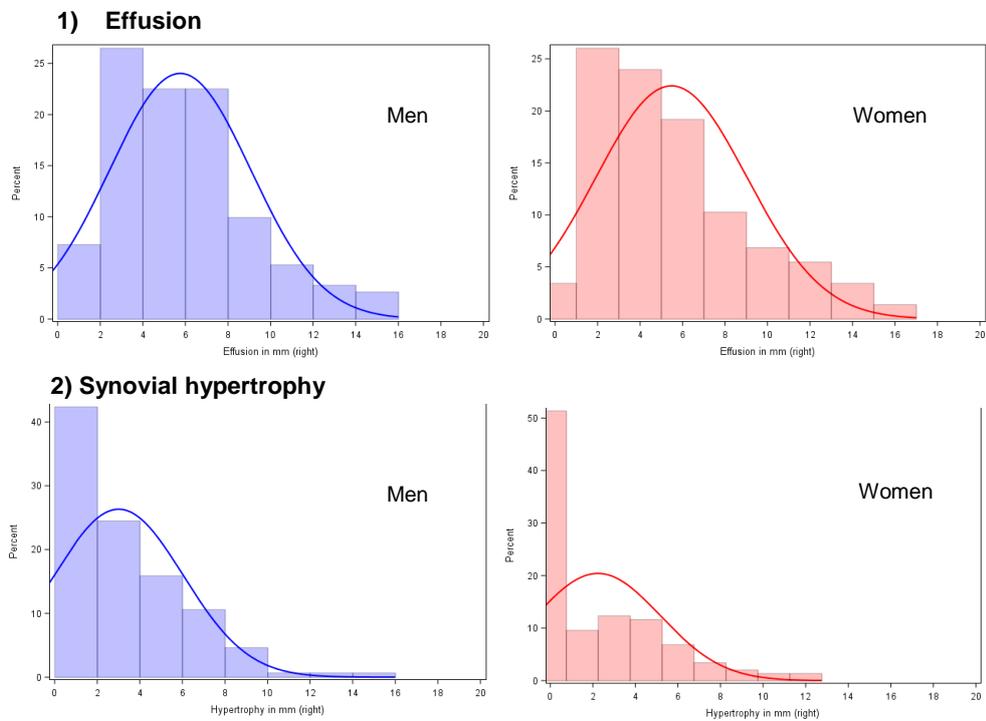


Figure 3-5. Raw distribution by gender of US effusion and hypertrophy

The participants for this study were divided into 4 groups according to their current knee pain and ROA status. Approximately half of recruited men and women had neither knee pain nor ROA (59% men; 52% women). Having knee pain without any structural changes on knee radiographs was present in 19% of men and 15% of women, whereas 13% of men and 15% of women had ROA without knee pain. There was a significant difference in the prevalence of current knee pain with co-existing ROA in men compared to women (9% vs 18%, respectively, $p=0.03$). The distribution curves for both effusion and synovial hypertrophy are presented in Figure 3-6.

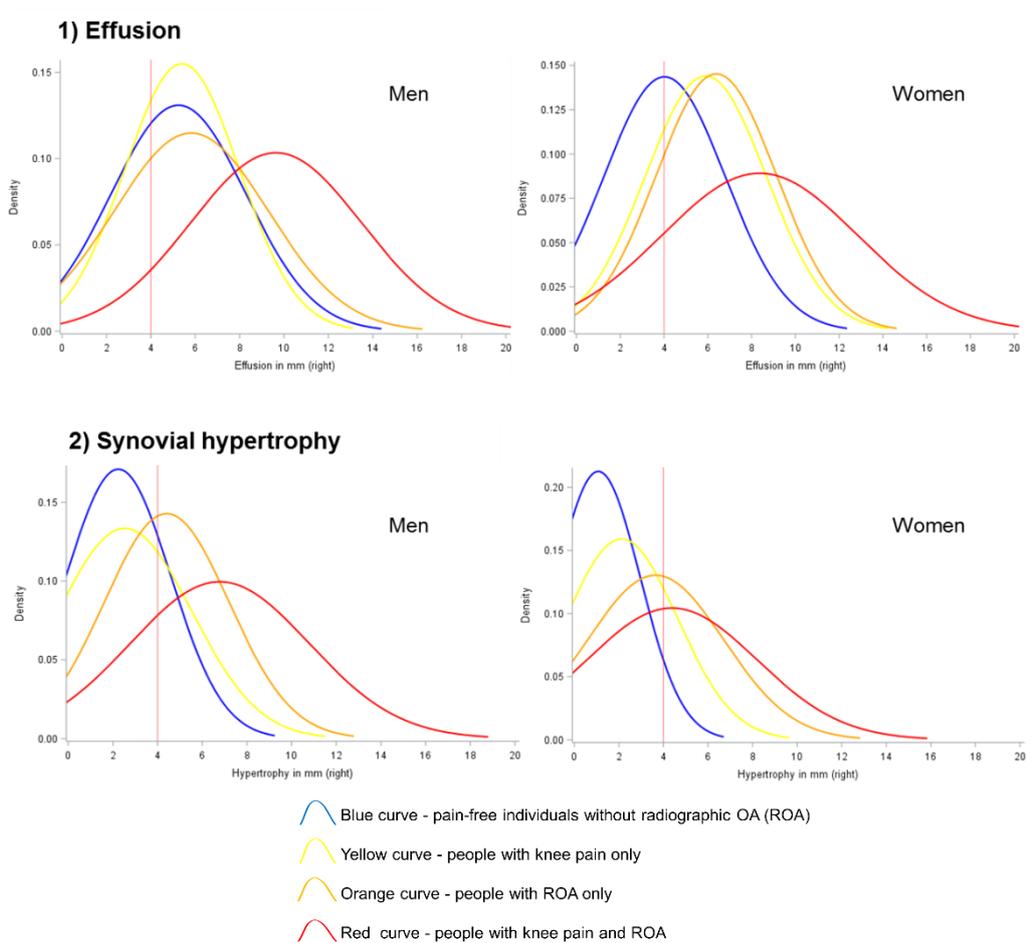


Figure 3-6. The distribution of effusion and synovial hypertrophy in sub-groups divided by knee pain and presence of radiographic knee osteoarthritis

Note: The red line represents the current threshold for abnormality (4 mm).

3.3.3. Mean and distribution of synovial changes detected on US by age, gender and laterality

Of the total 299, 163 individuals had no knee pain and ROA (88 men and 75 women). In this sample we explored the normal range and difference in US features by age, gender and laterality.

Age. For this analysis, we calculated mean and corresponding 95% intervals for both US measures in men and women in three age groups (40-55 years old, 55-70 years old and 70-85 years old). Both effusion and synovial hypertrophy did not associate with age (all p-values for linear trend >0.05) (Figure 3-7).

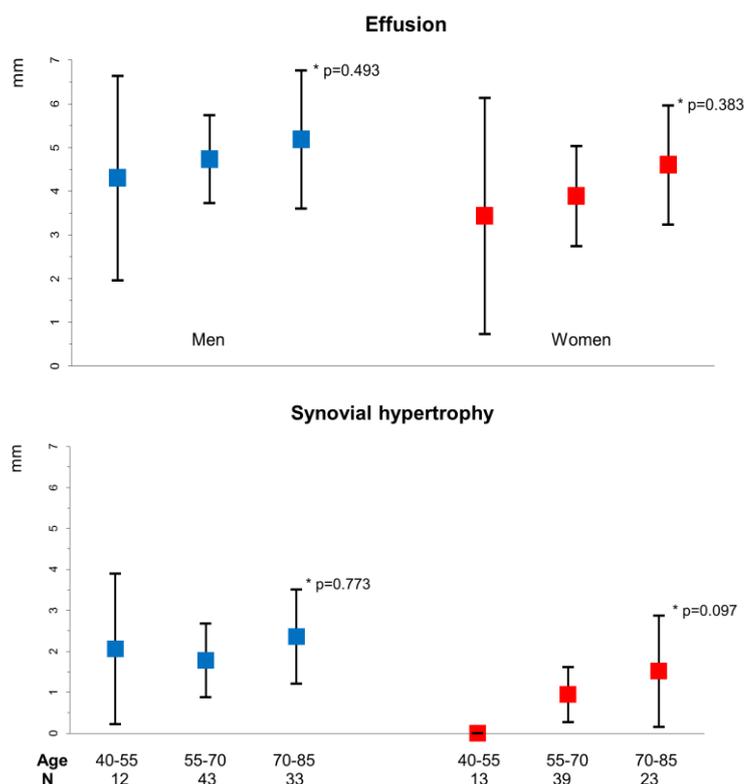


Figure 3-7. The mean US measures of effusion and hypertrophy in mm (95% CI) in men and women - comparison across different age groups
 Note: *P-value for trend.

Gender difference. Measures for effusion (mean 5.2 mm in men vs 4.0 mm in women for the right knee) and synovial hypertrophy (mean 2.2 mm in men vs 1.1 mm in women for the right knee) were both greater in men than in women.

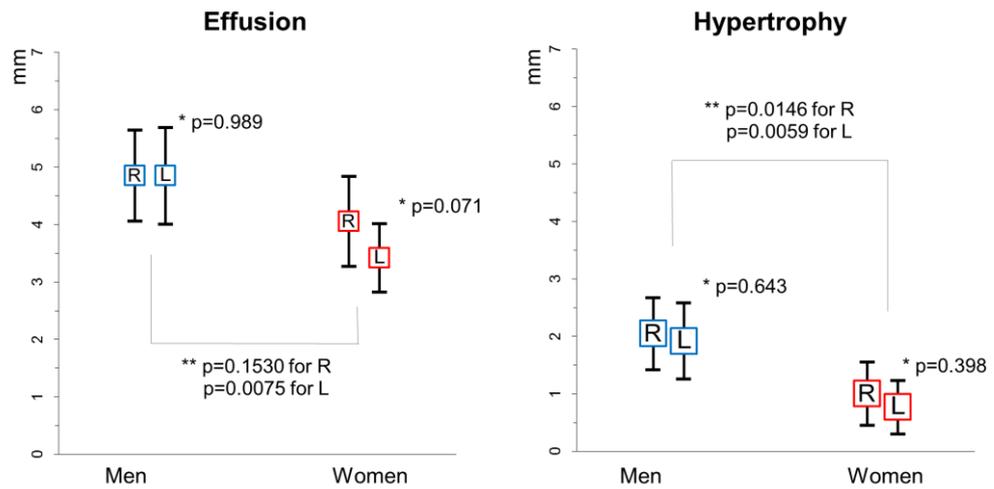


Figure 3-8. The mean US measures of effusion and hypertrophy in mm (95% CI) in men and women - comparison between right and left knees

Note: R - right knee; L - left knee;

* P-value for the difference between right and left knees (paired t-test);

** P-value for the difference between genders (independent t-test).

Laterality. There was no difference between right and left knees in both men and women (all $p > 0.05$, Figure 3-8).

3.3.4. Normal range of effusion and synovial hypertrophy

Depth of effusion ranged from 0 to 14.6 mm in men and from 0 to 13.3 in women. The mean depth of effusion was 5.24 mm (SD 3.05) in men and 4.02 mm (SD 2.78) in women. Synovial thickness ranged from 0 to 8.2 mm (mean 2.24 mm, SD 2.33) in men and from 0 to 8.0 mm (mean 1.08 mm, SD 1.88) in women. The prevalence of PDS was low (1% in men and 0% in women).

The upper limit was for effusion ≤ 10.3 mm in men and ≤ 9.8 mm in women, and for synovial hypertrophy ≤ 6.8 mm in men and ≤ 5.5 mm in women. The upper limits for effusion and for synovial hypertrophy with corresponding 95% CI are summarised in Table 3-12 and visually presented in Figure 3-9.

Table 3-12. Normal range in people without KP and ROA

	Upper limit (95% CI) for normal range, mm	
	Men (n=88)	Women (n=75)
Effusion	10.3 (9.3; 14.6)	9.3 (7.4; 13.3)
Synovial hypertrophy	6.8 (5.8; 8.2)	5.4 (3.9; 8.0)

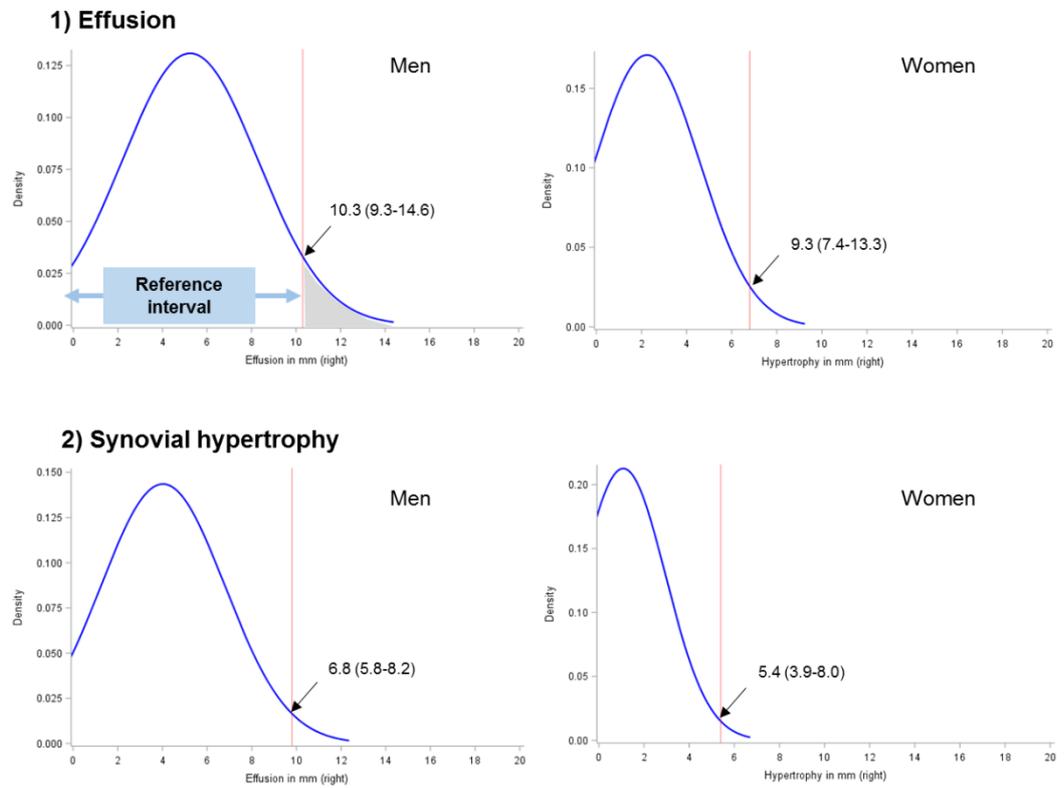


Figure 3-9. The distribution of effusion and synovial hypertrophy in pain-free individuals without osteoarthritic changes on knee x-rays
 Note: The red line represents an upper reference limit with 95% confidence intervals (CI).

3.3.5. Different thresholds: exploring misclassification rate

3.3.5.1. EULAR threshold

We examined how well the current threshold of 4 mm (D'Agostino et al., 2005) separates pain-free people without ROA from people with knee pain and ROA. For effusion the sensitivity of this threshold was good (93% and 79% for men and women, respectively). However, the specificity was poor (39% and 61%, respectively). Consequently, 60% of men and 39% of women without knee pain and ROA were classified as having the outcome (false-positive), and 7% of both men and 21% of women with knee pain and ROA were classified as non-disease (false-negative). For hypertrophy the sensitivity was poor (64% and 50% for men and women, respectively), while the specificity was good (78% and 89%, respectively). The proportion of men and women with false-positive and false-negative results is shown in Figure 3-10.

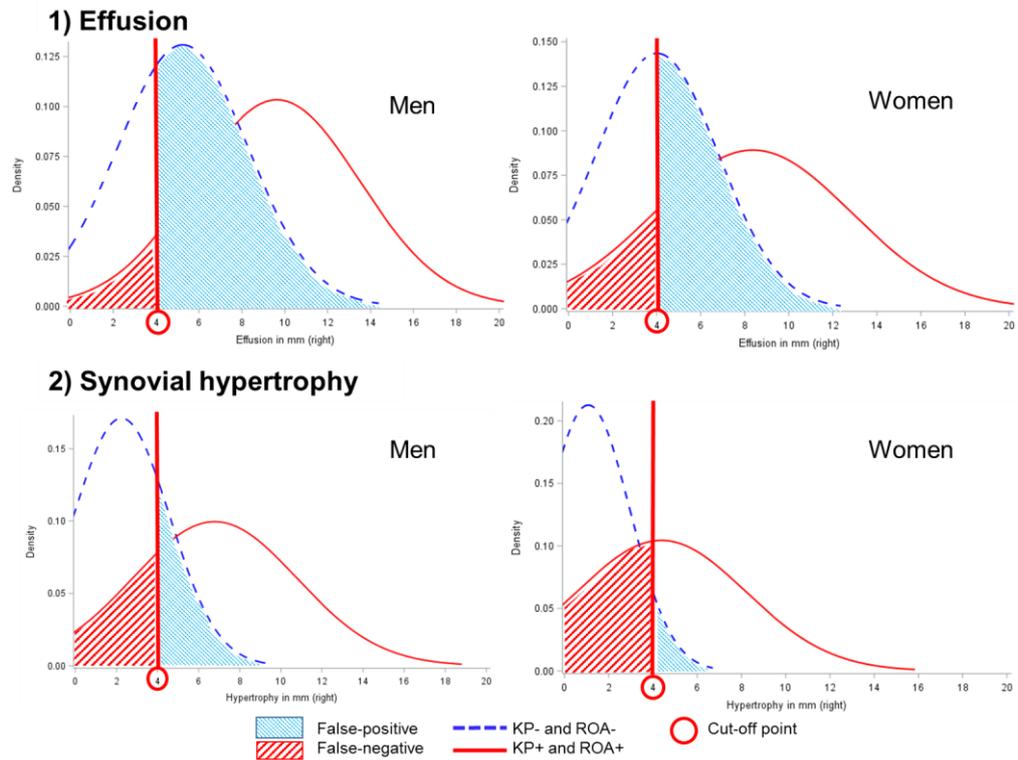


Figure 3-10. The probability density functions of a continuous value of effusion and hypertrophy for people with knee pain and radiographic osteoarthritis and pain-free people without radiographic osteoarthritis

The cut-off value is represented by the vertical red line. All test values equal or greater than this value are considered positive, otherwise they are considered negative. The area under the density functions shaded with red diagonal lines to the left of the cut-off value is the False-negative rate, and the area shaded in blue to the right of the cut-off value is the False-positive rate.

3.3.5.2. Threshold with the maximum sensitivity and specificity

In this analysis US measurements from people with a normal knee (no pain, no ROA) were plotted against the measurements from all people diagnosed with abnormal knees (knee pain plus ROA). The ROC curves are shown in Figure 3-11.

Based on the maximum value of the Youden Index the optimal threshold for effusion is 7.4 mm in men and 5.3 mm in women, and for synovial hypertrophy it is 3.7 for men and 1.6 for women. ROC analysis confirmed these results and revealed that the new cut-off points are characterised by the larger AUC and therefore better discriminative power. Cut-off values with corresponding sensitivity, specificity, AUC and other measures of diagnostic accuracy are presented in Table 3-13.

3.3.5.3. Threshold with high specificity

For effusion the threshold corresponding with specificity of 90% was 8.9 mm in men and 7.8 mm in women. Applying this threshold, only approximately 10% of controls had effusion above this threshold. For synovial hypertrophy the threshold corresponding with high specificity was 5.8 in men and 4.2 in women. The AUC for these cut-off values was greater than 0.7 (moderate discrimination ability) and LR+ are close to 5 (higher than LR+ for other cut-offs) (Table 3-13).

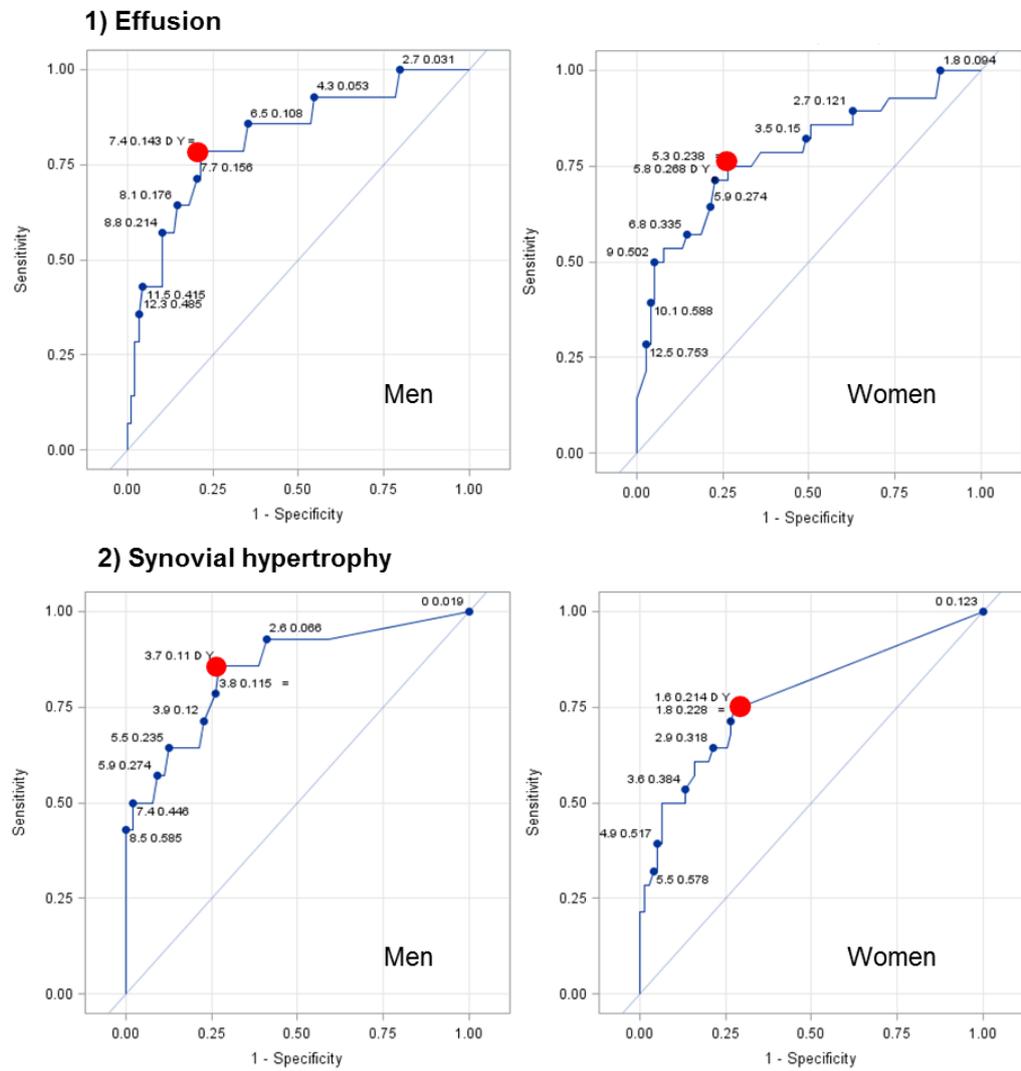


Figure 3-11. ROC curves for a continuous value of effusion and hypertrophy in men and women for discriminating people with knee pain and radiographic osteoarthritis from pain-free people without radiographic osteoarthritis

Note: The red dot represents an optimal cut-off value with the highest Youden Index.

Table 3-13. Sensitivity, specificity, positive and negative likelihood ratio of synovial effusion and hypertrophy for the diagnosis of knee abnormality according to the different thresholds

Criterion	Cut-off (mm)	Description	Positive in KP+ROA group, n/N(%)	Positive in controls, n/N(%)	AUC	Sensitivity (95%CI)	Specificity (95%CI)	J	LR+	LR-	FPP	FNP
Effusion												
men	4	Current	13/14 (92.86)	54/88 (61.36)	0.66 (0.57; 0.74)	0.93 (0.66; 1.00)	0.39 (0.28; 0.50)	0.31	1.51	0.18	0.81	0.03
	7.4	Optimal	11/14 (78.57)	19/88 (21.54)	0.79 (0.67; 0.91)	0.79 (0.49; 0.95)	0.78 (0.68; 0.86)	0.57	3.64	0.27	0.63	0.04
	8.9	High specificity	7/14 (50)	9/88 (10.23)	0.70 (0.56; 0.84)	0.50 (0.23; 0.77)	0.90 (0.81; 0.95)	0.40	4.89	0.56	0.56	0.08
women	4	Current	22/28 (78.57)	29/75 (38.67)	0.70 (0.60; 0.80)	0.79 (0.59; 0.92)	0.61 (0.49; 0.72)	0.40	2.03	0.35	0.57	0.12
	5.3	Optimal	14/28 (50)	8/75 (10.67)	0.71 (0.62; 0.81)	0.75 (0.55; 0.89)	0.73 (0.62; 0.83)	0.48	2.81	0.34	0.49	0.11
	7.8	High specificity	15/28 (53.57)	7/75 (9.33)	0.72 (0.62; 0.82)	0.54 (0.34; 0.72)	0.91 (0.82; 0.96)	0.44	5.74	0.51	0.32	0.16
Hypertrophy												
men	4	Current	9/14 (64.29)	19/88 (21.59)	0.71 (0.58; 0.85)	0.64 (0.35; 0.87)	0.78 (0.68; 0.86)	0.43	2.98	0.46	0.68	0.07
	3.7	Optimal	12/14 (85.71)	24/88 (27.27)	0.77 (0.66; 0.88)	0.86 (0.57; 0.98)	0.73 (0.62; 0.82)	0.58	3.14	0.20	0.67	0.03
	5.8	High specificity	8/14 (57)	9/88 (10.23)	0.74 (0.60; 0.87)	0.57 (0.29; 0.82)	0.90 (0.81; 0.95)	0.47	5.59	0.48	0.53	0.07
women	4	Current	21/28 (75)	20/75 (26.67)	0.70 (0.60; 0.80)	0.50 (0.31; 0.69)	0.89 (0.80; 0.95)	0.39	4.69	0.56	0.36	0.17
	1.6	Optimal	21/28 (75)	21/75 (28)	0.74 (0.64; 0.83)	0.75 (0.55; 0.89)	0.72 (0.60; 0.82)	0.47	2.68	0.35	0.50	0.11
	4.2	High specificity	14/28 (50)	7/75 (9.33)	0.70 (0.60; 0.80)	0.50 (0.31; 0.69)	0.91 (0.82; 0.96)	0.41	5.36	0.55	0.33	0.17

Note: AUC – area under the curve; CI – confidence interval; J – Youden Index; “LR+” - likelihood ratio of a positive test result; “LR-” - likelihood ratio of a negative test result; FPP – false positive probability; FNP – false negative probability.

3.3.6. Other associations

Association of synovial changes detected on US with knee pain. The prevalence of current knee pain was 37% in men and 41% in women. In men, the mean effusion was 6.39 mm in people with knee pain and 4.87 in those without knee pain regardless of ROA ($p=0.005$). In women, the mean effusion was 5.97 mm and 4.78 in those with and without knee pain ($p=0.048$). The mean synovial hypertrophy was 3.54 mm vs 2.27 mm respectively in men and 2.69 mm vs 1.58 mm in women. Thus, individuals reporting knee pain (regardless of ROA) had higher values of synovial hypertrophy compared to those without KP (all $p<0.05$) (Figure 3-12).

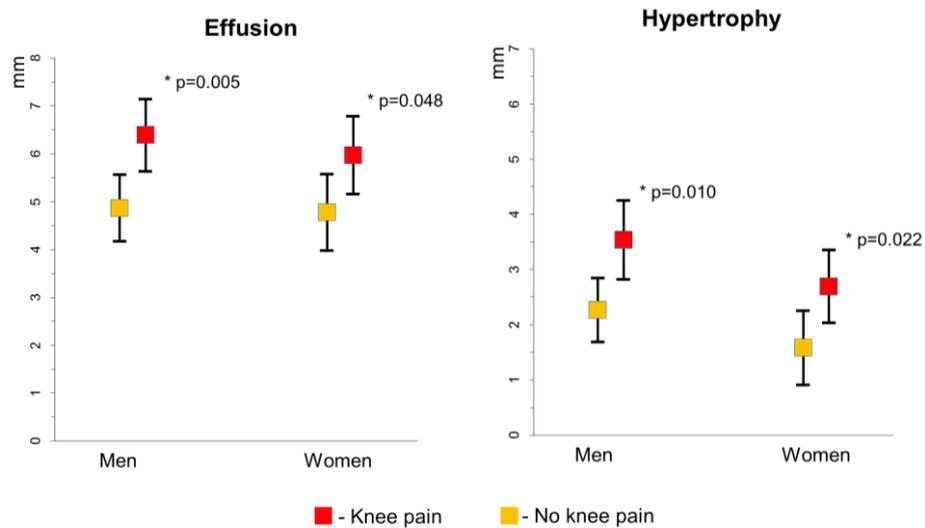


Figure 3-12. Mean effusion and hypertrophy in mm (95% CI) in men and women - comparison between people with and without knee pain

Note: * P-value for the difference between KP and no KP (independent t-test).

Association of synovial changes detected on US with global radiographic score. Both effusion and synovial hypertrophy moderately correlated with global radiographic score in the same knee ($r_p=0.41$ and $r_p=0.51$ for effusion in the right and left knee, and $r_p=0.49$ and $r_p=0.50$ for synovial hypertrophy respectively). The mean depth of effusion and synovial thickness gradually increased with increasing radiographic severity when global radiographic score was categorised as “less than 5”, “from 5 to 10”, “from 10 to 15” and “15 and more” (all p for trend <0.001) (Figure 3-13).

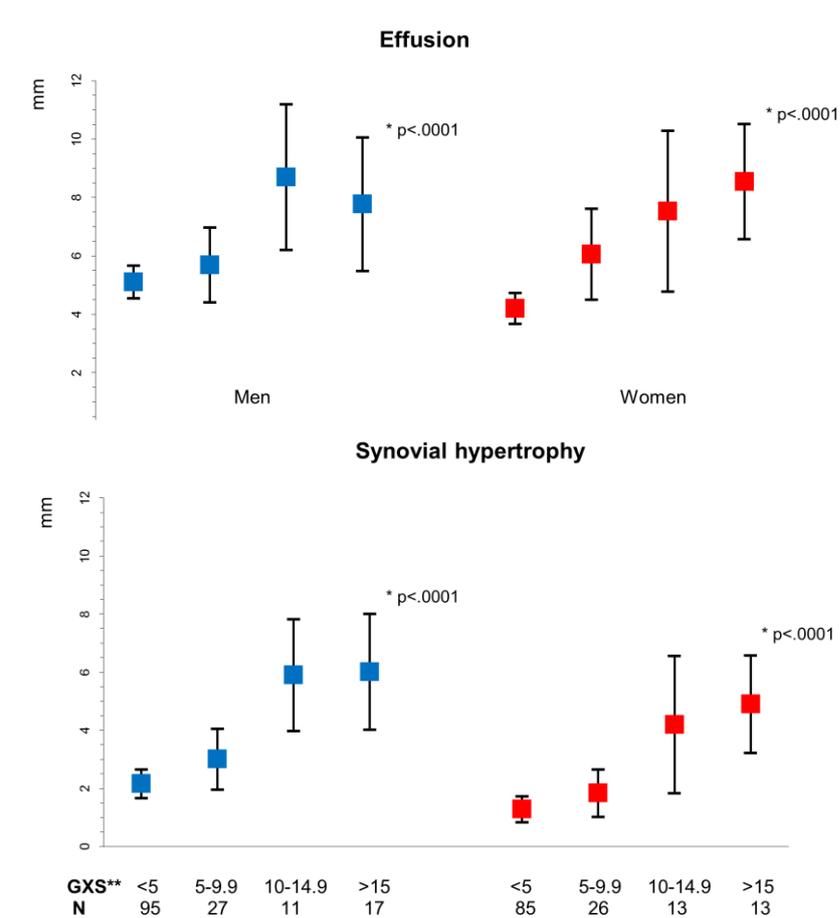


Figure 3-13. Mean effusion and hypertrophy in mm (95% CI) in men and women - comparison across different radiographic severity groups

Note: * P-value for trend;

** For global radiographic score (horizontal axis), the scale was categorised as “less than 5”, “from 5 to 10”, “from 10 to 15” and “15 and more”

3.3.7. Summary

The analyses presented in this section (3.3) describe the distribution and normal range for effusion and synovial hypertrophy, and the optimal cut-offs between normal population and people with knee pain plus ROA. This study demonstrates that there is a significant difference in US values between men and women. The upper normal range limit for effusion was calculated to be at 10.3 mm in men and ≤ 9.8 mm in women, and for synovial hypertrophy at 6.8 mm in men and ≤ 5.5 mm in women (Figure 3-9). These values are greater than the currently accepted threshold for US abnormality (4 mm). This explains to some extent the high misclassification rate revealed by our analysis (Figure 3-10). However, it is not easy to identify an optimal threshold for effusion and synovial hypertrophy as the distribution curves for people with and without knee pain and ROA largely overlap (Figure 3-6).

Two methods were used to identify an optimal threshold. Firstly, the Youden index which gave cut-off values with the maximum sensitivity and specificity. Secondly, we calculated the threshold that gave 90% specificity for separating people with knee pain and ROA. The diagnostic accuracy for all three thresholds (including the current threshold of 4 mm) was summarised and presented at the end of the section (Table 3-13).

3.4. Association between ultrasound-detected synovitis and knee pain: a population-based case-control study with both cross-sectional and follow-up data

3.4.1. Baseline cross-sectional study

3.4.1.1. Demographic and clinical characteristics of the study population

At baseline 495 participants were recruited, of whom 298 had early knee pain, 103 established KP and 94 no knee pain. Of those with early knee pain, 219 were recruited at baseline and 79 were incident cases identified during follow-up. Age and gender were equally distributed among the three groups. However, a graded increase from no knee pain to early knee pain, then to established knee pain groups was observed for BMI, pain severity, ROA, and use of analgesics (Table 3-14).

Table 3-14. Characteristics of the study population: three-group comparison

	No knee pain	Early knee pain	Established knee pain	p-value
N	94	298	103	
Age (years), mean (SD)	60.98 (9.81)	61.42 (9.66)	59.53 (10.04)	0.2992*
Women, n (%)	58 (61.70)	179 (60.07)	63 (61.17)	0.9509**
BMI (kg/m²), mean (SD)	26.78 (4.49)	28.85 (5.70)	31.96 (6.49)	<.0001*
Current knee pain¹ severity (NRS 0-10), mean (SD)		4.55 (2.52)	7.40 (2.14)	<.0001 [†]
Power Doppler Signal, n (%)		10 (3.36)	2 (1.94)	0.4261 [‡]
Radiographic OA², n (%)	7 (7.45)	80 (26.85)	49 (47.57)	<.0001**
Global radiographic score³ (0-60), mean (SD)	2.24 (3.08)	5.72 (7.00)	11.28 (9.26)	<.0001*
Muscle strength (kg, lowest tertile⁴), n (%)				
<i>Quadriceps strength</i>	33 (35.11)	99 (33.22)	65 (63.11)	<.0001**
<i>Hip abductor strength</i>	33 (35.11)	119 (39.93)	68 (66.02)	<.0001**
Use of analgesics, n (%)				
<i>Prescribed NSAIDs</i>	3 (3.19)	19 (6.38)	15 (14.56)	0.0018
<i>Opioids</i>	3 (3.19)	44 (14.77)	22 (21.36)	0.0005
<i>Over-the-counter NSAIDs</i>	12 (12.77)	68 (22.82)	32 (31.07)	0.0021

Note: [†] t-test; [‡] x2 test; * test for linear trend; ** Cochran-Armitage trend test for trend.

Groups were matched by age and gender.

SD - standard deviation; NRS – numerical rating scale 0-10; BMI - body mass index; OA – osteoarthritis; NSAIDs - non-steroidal anti-inflammatory drugs.

¹ Knee pain on most days of the past month.

² Radiographic OA defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

³ Summated score for osteophytes and joint space narrowing (NLDLDA scoring system) in tibiofemoral and patofemoral joints (medial and lateral compartments).

⁴ Lowest tertile values for muscle strength tests: quadriceps strength <17.6 kg for men and <10.7 kg for women; hip abductor strength <12.8 kg and <8.2 kg, respectively.

3.4.1.2. US synovial features and their association with knee pain

Effusion ≥ 4 mm was associated with knee pain, but this association diminished after adjustment for age, gender, BMI, ROA severity and quadriceps strength (Table 3-15). Synovial hypertrophy also associated with KP and this association remained statistically significant after the adjustment. Adjusted ORs (95%CI) were 3.18 (1.18 to 8.57) for early knee pain and 5.07 (1.70 to 15.12) for established knee pain. There was a stronger association between ROA and knee pain (age, gender, BMI-adjusted ORs 4.37, 95%CI 1.89 to 10.13, and 11.82, 95%CI 4.71 to 29.66) for early and established knee pain respectively), that was not diminished with the adjustment for confounding factors including synovial hypertrophy. Additional adjustment for analgesic use and quadriceps strength did not change the strength of association (Appendix 11).

Table 3-15. Ultrasound synovial features at baseline and associations with knee pain

	No Knee Pain	Early Knee Pain	Established Knee Pain
Effusion			
<i>mean in mm (SD)</i>	3.02 (2.10)	4.48 (3.64)	5.89 (3.48)
≥ 4 mm, n (%)	23 (24.47)	136 (45.64)	64 (62.14)
≥ 4 mm OR (95%CI)	1	2.64 (1.57; 4.45)	5.07 (2.74; 9.38)
≥ 4 mm aOR (95%CI)		1.96 (1.10; 3.49)	2.05 (0.98; 4.26)
Synovial hypertrophy			
<i>mean in mm (SD)</i>	0.65 (1.56)	2.01 (2.66)	3.57 (3.49)
≥ 4 mm, n (%)	5 (5.32)	69 (23.15)	44 (42.72)
≥ 4 mm OR (95%CI)	1	5.43 (2.12; 13.92)	13.27 (4.97; 35.43)
≥ 4 mm aOR (95%CI)		3.18 (1.18; 8.57)	5.07 (1.70; 15.12)
Power Doppler Signal			
n (%)	0	10 (3.36)	2 (1.94)

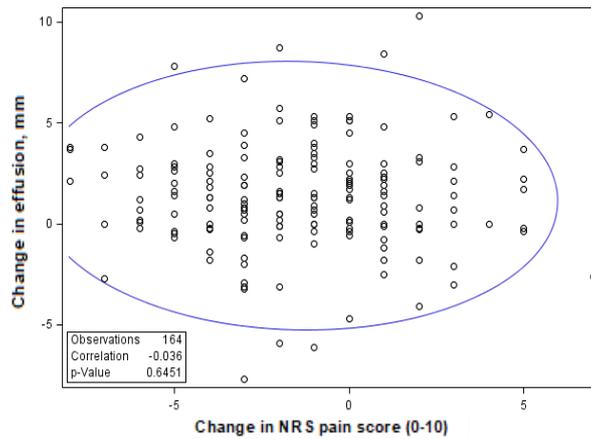
Note: aOR: odds ratios adjusted for age, gender, BMI, quadriceps strength and radiographic OA scores.

3.4.2. One year follow-up study

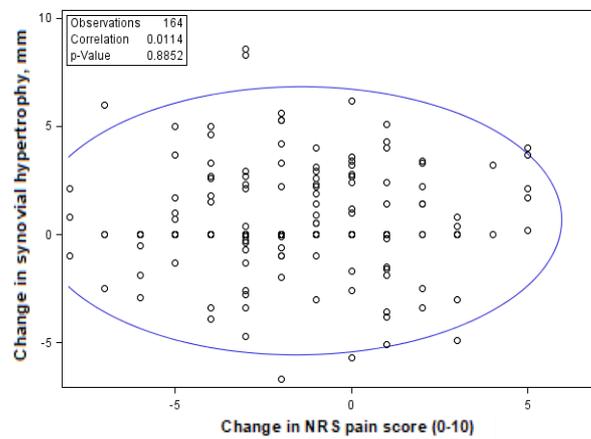
3.4.2.1. Correlation between ultrasound changes and knee pain changes

Of 219 participants with early knee pain at baseline, 166 (76%) completed the 1 year follow-up US assessment. The NRS pain score decreased from 4.44 at baseline to 2.99 at one year ($p < 0.0001$). However, the mean depth of effusion and hypertrophy increased from 3.98 mm to 5.35 mm, and from 1.80 mm to 2.44 mm, respectively (both $p < 0.0001$). There was no correlation between change in NRS pain scores and change in effusion or synovial hypertrophy ($r_p = -0.04$ and $r_p = 0.01$ for effusion and synovial hypertrophy respectively). Scatter plots were used to illustrate the non-linear relationships between US changes and knee pain changes compared to the linear relationship observed between change in effusion and change in synovial hypertrophy (Figure 3-14).

1) Effusion vs NRS pain



2) Hværtrohv vs NRS pain



3) Effusion vs synovial hværtrohv

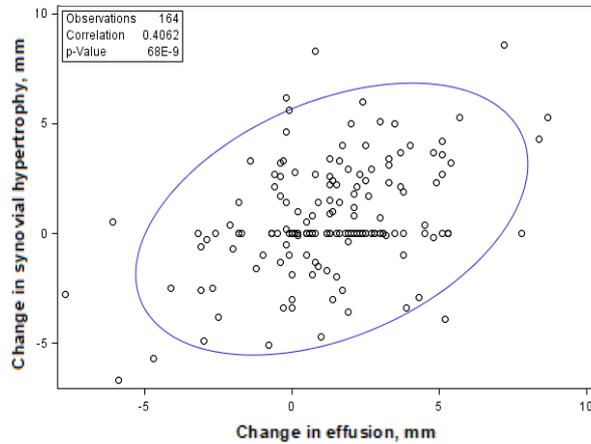


Figure 3-14. Scatter plots showing correlation between changes in pain score versus changes in effusion/hypertrophy and changes in effusion versus changes in synovial hypertrophy.

Note: with 95% prediction ellipses; NRS – numeric rating scale (0-10).

3.4.2.2. Baseline predictors of changes in pain

After one year, according to the PGA of knee pain change, 18% of people with early knee pain reported that their pain had worsened (n=32 out of 181) and 42% of people with established knee pain reported worsening of pain (n=31 out of 74).

Both effusion and ROA predicted worsening of knee pain after adjustment for age, gender, and BMI (aOR 1.95, 95% CI 1.05 to 3.64 for effusion and aOR 4.73 95%CI 2.46 to 9.10 for ROA) (Table 3-16). However, the association between effusion and worsening of knee pain diminished after further adjustment for radiographic severity (aORs 0.99, 95%CI 0.90 to 1.10, and 0.95, 95%CI 0.44 to 2.02, for effusion in mm and effusion \geq 4mm respectively).

Table 3-16. Association between baseline risk factors and worsening of knee pain

	Descriptive		ORs (95% CI)	
	Stable/ Improved	Worsened	Crude	Age, gender, BMI-adjusted
N	192	63		
Effusion				
<i>Mean in mm (SD)</i>	4.24 (3.44)	6.20 (4.09)	1.15 (1.06; 1.24)	1.11 (1.02; 1.20)
<i>Effusion\geq4mm, n (%)</i>	79 (41.58)	40 (63.49)	2.44 (1.36; 4.40)	1.95 (1.05; 3.64)
Synovial hypertrophy				
<i>Mean in mm (SD)</i>	2.06 (2.89)	3.35 (3.35)	1.14 (1.04; 1.24)	1.09 (0.99; 1.20)
<i>Thickness\geq4mm, n (%)</i>	45 (23.68)	24 (38.10)	1.98 (1.08; 3.64)	1.40 (0.72; 2.74)
Power Doppler Signal, n (%)	8 (4.17)	1 (1.59)	0.37 (0.05; 3.03)	0.47 (0.06; 4.02)
Global radiographic score (0-60), mean (SD)	5.81 (7.19)	13.58 (9.40)	1.11 (1.07; 1.15)	1.10 (1.06; 1.14)
Radiographic OA, n (%)	44 (23.16)	39 (62.90)	5.63 (3.04; 10.41)	4.73 (2.46; 9.10)

Note: Significant associations are highlighted in bold.

OA – osteoarthritis; SD – standard deviation; BMI – body mass index; ORs –odds ratios; CI – confidence interval.

The sensitivity analysis using any increase from baseline in NRS for knee pain showed that no baseline risk factors predicted increased knee pain (Table 3-17).

Table 3-17. Association between baseline risk factors and increase in pain severity (NRS 0-10)

	Descriptive		ORs (95% CI)	
	Stable/ Improved	Worsened	Crude	Age, gender, BMI-adjusted
N	193	62		
Effusion				
<i>Mean in mm (SD)</i>	4.70 (3.67)	4.80 (3.83)	1.01 (0.93; 1.09)	1.01 (0.92; 1.09)
<i>Effusion≥4mm, n (%)</i>	88 (45.83)	31 (50.82)	1.22 (0.69; 2.17)	1.15 (0.62; 2.13)
Synovial hypertrophy				
<i>Mean in mm (SD)</i>	2.34 (3.04)	2.52 (3.12)	1.02 (0.93; 1.12)	1.02 (0.92; 1.13)
<i>Thickness≥4mm, n (%)</i>	50 (26.04)	19 (31.15)	1.28 (0.68; 2.41)	1.29 (0.64; 2.60)
Power Doppler Signal, n (%)	6 (3.11)	3 (4.84)	1.59 (0.38; 6.53)	1.55 (0.36; 6.63)
Global x-ray score (0-60), mean (SD)	7.55 (8.55)	8.27 (8.24)	1.01 (0.98; 1.04)	1.01 (0.97; 1.05)
Radiographic OA, n (%)	59 (30.73)	24 (40.00)	1.50 (0.82; 2.74)	1.53 (0.80; 2.94)

Note: OA – osteoarthritis; SD – standard deviation; BMI – body mass index; ORs – odds ratios; CI – confidence interval.

3.4.3. Highly specific threshold for effusion and synovial hypertrophy

Analysis for the association between knee pain and US measures (at baseline and follow-up) was repeated for the highly specific thresholds established in the previous study (Section 3.3). At baseline, the prevalence of effusion greater than 8.9 mm in men and 7.8 mm in women was 13% in people with early knee pain and 27% in people with established knee pain. The prevalence of synovial hypertrophy greater than 5.8 mm in men and 4.2 mm in women was 17% in people with early knee pain and 36% in people with established knee pain (Table 3-18). After adjustment for age, gender, BMI, quadriceps strength and radiographic severity the association was significant only between synovial hypertrophy and established knee pain (OR 4.37, 95% 1.33 to 14.35). At follow-up, neither baseline effusion nor baseline synovial hypertrophy predicted worsening of knee pain (Table 3-19).

Table 3-18. Ultrasound synovial features at baseline according to the highly specific threshold and their associations with knee pain

	No Knee Pain (n=94)	Early Knee Pain (n=298)	Established Knee Pain (n=103)
Effusion (present/absent)*			
<i>N (%)</i>	3 (3.19)	40 (13.42)	28 (27.18)
<i>OR (95%CI)</i>	1	4.76 (1.44; 15.76)	11.32 (3.31; 38.71)
<i>aOR (95%CI)</i>		2.39 (0.67; 8.49)	2.17 (0.54; 8.72)
Synovial hypertrophy (present/absent)**			
<i>N (%)</i>	4 (4.26)	50 (16.78)	37 (35.92)
<i>OR (95%CI)</i>	1	4.59 (1.61; 13.08)	12.61 (4.29; 37.12)
<i>aOR (95%CI)</i>		2.60 (0.86; 7.82)	4.37 (1.33; 14.35)

Note: * threshold for effusion was 8.9 mm in men and 7.8 mm in women;
 ** threshold for synovial hypertrophy 5.8 mm in men and 4.2 mm in women.

OR – crude odds ratio; aOR: odds ratios adjusted for age, gender, BMI, quadriceps strength and radiographic osteoarthritis scores; CI –confidence interval.

Table 3-19. Association between baseline ultrasound synovial features according to the highly specific threshold and worsening of knee pain

	Improved/stable (n=139)	Worsened (n=27)
Baseline effusion (present/absent)*		
<i>N (%)</i>	26 (13.68)	19 (30.16)
<i>OR (95%CI)</i>	1	2.72 (1.38; 5.37)
<i>aOR (95%CI)</i>	1	1.88 (0.91; 3.89)
Baseline hypertrophy (present/absent)**		
<i>N (%)</i>	32 (16.84)	19 (30.16)
<i>OR (95%CI)</i>	1	2.13 (1.10; 4.12)
<i>aOR (95%CI)</i>	1	1.48 (0.72; 3.01)

Note: * threshold for effusion was 8.9 mm in men and 7.8 mm in women;
 ** - threshold for synovial hypertrophy 5.8 mm in men and 4.2 mm in women.

OR – crude odds ratio; aOR: odds ratios adjusted for age, gender, BMI, quadriceps strength and radiographic osteoarthritis scores; CI –confidence interval.

3.4.4. Other results: ultrasound features and radiographic changes

At baseline both effusion and synovial hypertrophy showed dose-response relationships with global radiographic scores (Figure 3-15). After adjusting for all other confounding factors regression coefficients were 0.21 (95% CI 0.17 to 0.25) for effusion and 0.17 (95% CI 0.13 to 0.20) for synovial hypertrophy (both $p < 0.0001$).

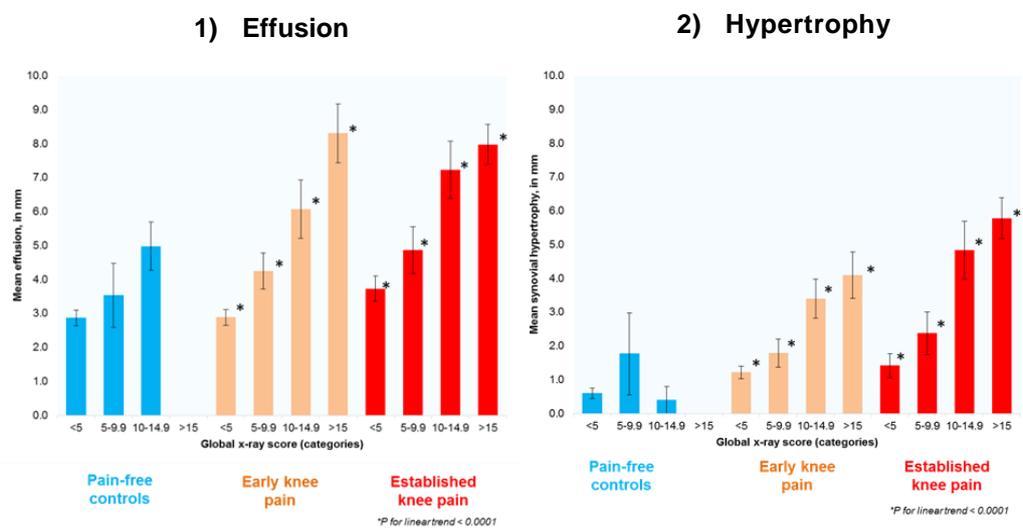


Figure 3-15. Bar chart showing mean effusion and mean synovial hypertrophy for each group

Note: For global radiographic score (horizontal axis), the scale was categorised as <5, 5 to 9.99, 10 to 14.99, and >15. Vertical error bars indicate standard error of the mean

At one year radiographic baseline score did not predict change in effusion or synovial hypertrophy (β -coefficient 0.03, 95% CI -0.02 to 0.08 for increase in effusion and β -coefficient 0.04, 95% CI -0.003 to 0.08 for increase in synovial hypertrophy).

3.4.5. Summary

This case-control study aimed to examine whether community-derived people with early or established knee pain are more likely to have synovial changes detected on US, specifically effusion, synovial hypertrophy and PDS, compared to pain-free controls and to explore whether synovial changes detected on US predict/associate with subsequent KP worsening. We found, firstly, that synovial changes detected on US were associated with knee pain but the association was confounded by ROA severity. Secondly, changes in synovial changes detected on US did not correlate with changes in knee pain over one-year. Thirdly, effusion and ROA severity but not synovial hypertrophy at baseline predicted knee pain worsening at one-year. Increasing the thresholds for effusion and synovial hypertrophy further reduced the association with and prediction for knee pain.

3.5. Contribution of central vs peripheral risk factors (including synovial changes on ultrasound) to knee pain and the role of synovitis in different types of pain

3.5.1. Demographic and clinical characteristics of the study population

A total of 736 participants (422 women, 314 men) were included in the analysis. The mean age was 62.65 (SD 9.96) years, 57% were women, and the mean BMI was 28.19 (SD 5.69). Prevalence of ever knee pain was 72% (men, 55%; women, 58%). People with knee pain used significantly more NSAIDs and opioids (8% vs 2% for prescribed NSAIDs, 27% vs 14% for over-the-counter NSAIDs and 15% vs 3% for opioids). The characteristics of the study population by knee pain are presented in Table 3-20. More than a half of the study population suffered from one or more coexistent diseases (59% in people with knee pain, 48% of those without knee pain). The most prevalent conditions in the knee pain participants were cardiovascular diseases (44%), non-restorative pain disorders (15%), and endocrine diseases (15%). The detailed results on comorbidity are presented in Appendix 12.

Table 3-20. Characteristics of the study population

	No knee pain	Knee pain	P-value
N	207	529	
Age (years), mean (SD)	64.51 (9.94)	61.92 (9.88)	0.0015
Women, n (%)	113 (54.59)	309 (58.41)	0.3458
BMI (kg/m²), mean (SD)	25.87 (4.40)	29.11 (5.87)	<.0001
Current knee pain¹, n (%)		384 (72.73)	
Current knee pain severity (NRS 0-10), mean (SD)		4.79 (2.94)	
Use of analgesics			
<i>Prescribed NSAIDs, n (%)</i>	5 (2.42)	40 (7.58)	0.0087
<i>Over-the-counter NSAIDs, n (%)</i>	28 (13.53)	143 (27.08)	<.0001
<i>Opioids, n (%)</i>	7 (3.38)	79 (14.96)	<.0001

Note: SD - standard deviation; NRS – numerical rating scale 0-10; BMI - body mass index; NSAIDs - non-steroidal anti-inflammatory drugs.

¹Knee pain on most days of the past month.

3.5.2. Risk factors associated with knee pain

Many central and peripheral risk factors associated with knee pain (Table 3-21). Among central risk factors the strongest association with prevalent knee pain was found for WSP (OR 2.76, 95% CI 1.72 to 4.42), followed by pain catastrophizing (OR 2.11, 95% CI 1.45 to 3.08 for PCS \geq 9) and then anxiety (OR 1.42, 95% CI 1.01 to 2.00 for HAD-A \geq 8). The peripheral risk factors associated with the presence of knee pain compared with no knee pain were ROA (OR 4.03, 95% CI 2.45 to 6.61), previous knee injury (OR 3.80, 95% CI 2.21 to 6.52), synovial hypertrophy (OR 2.91, 95% CI 1.83 to 4.64), effusion (OR 1.88, 95% CI 1.32 to 2.68) and high risk occupation (OR 1.47, 95% CI 1.02 to 2.11). Among other risk factors higher comorbidity count (OR 1.50, 95% CI 1.05 to 2.15 for the presence of any comorbidity) and BMI (OR 1.14, 95% CI 1.09 to 1.18) also associated with knee pain.

The relative contribution of central and peripheral risk factors is shown in Table 3-22. The AUC for the full model including central, peripheral and other factors was 0.80 (95% CI 0.77 to 0.84). The PRC of central factors to the full model was 5%, the contribution of peripheral factors was 25%, and the contribution of other risk factors was 12%. The contribution of central, peripheral and other risk factors to knee pain is visually displayed in Figure 3-16.

Table 3-21. Risk factors associated with knee pain

	Descriptive		ORs (95% CI)	
	No knee pain	Knee pain	Crude	Age, gender, BMI-adjusted
N	207	529		
CENTRAL RISK FACTORS				
Widespread pain ¹ , n (%)	25 (12.08)	168 (31.82)	3.40 (2.15; 5.36)	2.76 (1.72; 4.42)
HADS anxiety score ≥8, n (%)	84 (40.58)	272 (51.52)	1.56 (1.12; 2.15)	1.42 (1.01; 2.00)
HADS depression score ≥8, n (%)	105 (50.72)	251 (47.54)	0.88 (0.64; 1.21)	0.97 (0.69; 1.36)
PCS (highest tertile ≥9), n (%)	50 (24.15)	233 (44.13)	2.48 (1.73; 3.56)	2.11 (1.45; 3.08)
PERIPHERAL RISK FACTORS				
Significant injury, n (%)	18 (8.74)	125 (23.81)	3.26 (1.93; 5.51)	3.80 (2.21; 6.52)
Early life malalignment ² , n (%)	9 (4.59)	31 (6.09)	1.35 (0.63; 2.88)	1.50 (0.68; 3.30)
<i>varus</i> , n (%)	7 (3.61)	14 (2.86)	0.79 (0.31; 1.98)	0.99 (0.38; 2.56)
<i>valgus</i> , n (%)	2 (1.06)	17 (3.44)	3.33 (0.76; 14.55)	3.34 (0.73; 15.23)
Current malalignment, n (%)	1 (0.51)	28 (5.48)	11.30 (1.53; 83.66)	10.01 (1.33; 75.51)
<i>varus</i> , n (%)	0	10 (1.96)	n/a	n/a
<i>valgus</i> , n (%)	1 (0.51)	18 (3.52)	7.12 (0.94; 53.68)	5.69 (0.73; 44.23)
High risk occupation, n (%)	62 (29.95)	229 (43.29)	1.78 (1.27; 2.52)	1.47 (1.02; 2.11)
2D4D ratio (type 3), n (%)	121 (60.20)	264 (51.76)	0.71 (0.51; 0.99)	0.77 (0.54; 1.11)
Effusion				
<i>Mean in mm (SD)</i>	4.04 (2.65)	5.30 (3.80)	1.12 (1.06; 1.18)	1.13 (1.07; 1.20)
<i>Effusion ≥4mm, n (%)</i>	85 (41.06)	292 (55.62)	1.80 (1.30; 2.49)	1.88 (1.32; 2.68)
Synovial hypertrophy				
<i>Mean in mm (SD)</i>	1.39 (2.22)	2.63 (3.04)	1.20 (1.12; 1.28)	1.21 (1.12; 1.31)
<i>Thickness ≥4mm, n (%)</i>	28 (13.53)	164 (31.24)	2.90 (1.87; 4.50)	2.91 (1.83; 4.64)
Power Doppler Signal, n (%)	4 (1.93)	16 (3.03)	1.58 (0.52; 4.80)	2.56 (0.83; 7.90)
Global radiographic score (0-60) ³ , mean (SD)	2.89 (4.68)	7.42 (8.17)	1.13 (1.09; 1.17)	1.14 (1.10; 1.19)
Radiographic OA ⁴ , n (%)	24 (11.71)	174 (33.53)	3.80 (2.39; 6.04)	4.03 (2.45; 6.61)
OTHER RISK FACTORS				
Age, mean (SD)*	64.51 (9.94)	61.92 (9.88)	0.97 (0.96; 0.99)	0.98 (0.97; 1.00)
Women, n (%)**	113 (54.59)	309 (58.41)	1.17 (0.85; 1.61)	1.02 (0.73; 1.44)
BMI (kg/m ²), mean (SD)***	25.87 (4.40)	29.11 (5.87)	1.14 (1.10; 1.19)	1.14 (1.09; 1.18)
Nodal OA, n (%)	21 (10.29)	70 (13.70)	1.38 (0.82; 2.32)	1.58 (0.90; 2.77)
N of comorbidities, mean (SD)	0.65 (0.80)	0.85 (0.89)	1.32 (1.08; 1.61)	1.22 (0.98; 1.52)
Any comorbidities, n (%)	99 (47.83)	310 (58.60)	1.54 (1.12; 2.13)	1.50 (1.05; 2.15)
Any comorbidities ≥2, n (%)	29 (14.01)	109 (20.60)	1.59 (1.02; 2.49)	1.18 (0.73; 1.91)
Any comorbidities ≥3, n (%)	7 (3.38)	27 (5.10)	1.54 (0.66; 3.58)	1.03 (0.42; 2.54)
Any comorbidities ≥4, n (%)	0 (0.00)	3 (0.57)	n/a	n/a

Note: * adjusted for gender, BMI; ** adjusted for age, BMI; *** adjusted for age and gender.

Significant associations are highlighted in bold.

OR – odds ratio; CI – confidence interval; SD – standard deviation; HADS - Hospital Anxiety and Depression Scale; PCS - Pain Catastrophizing Scale.

¹ Concurrent pain experienced within the past 4 weeks axially, above and below the waist, and on both sides of the body (ACR criteria) self-reported using a diagrammatic manikin.

² Self-reported frontal plane knee alignment when the participant was aged in their 20's.

³ Radiographic osteoarthritis defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

⁴ Summated score for osteophytes and joint space narrowing (NLDLDA scoring system) in tibiofemoral and patello-femoral joints (medial and lateral compartments).

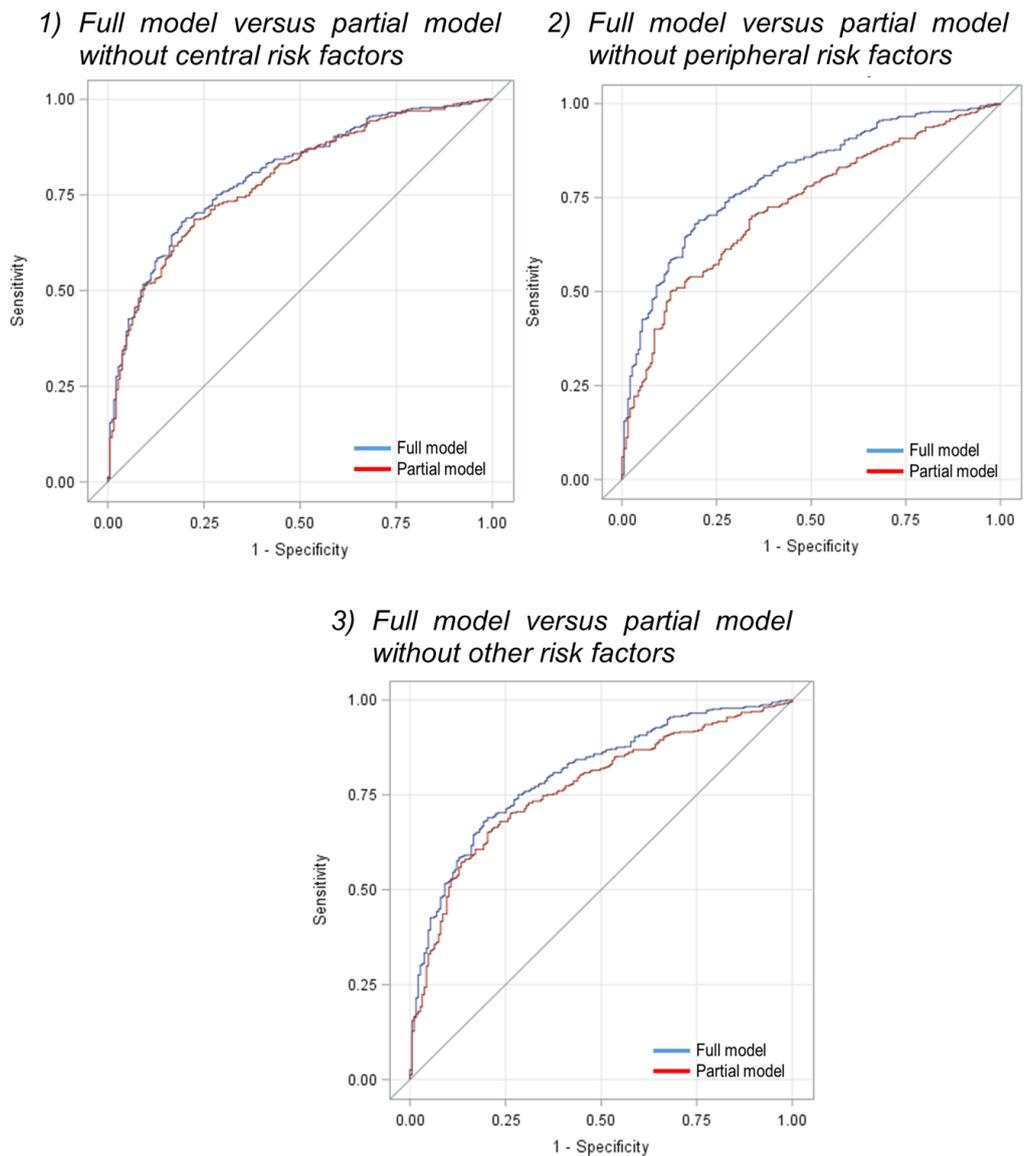


Figure 3-16. Receiver-operator-characteristic curves for risk factors for knee pain

Table 3-22 Receiver-operator-characteristic curves for risk factors for knee pain

Model	AUC (95%CI)	Proportional risk contribution (PRC)*
Full	0.8038 (0.7683; 0.8394)	100%
without central	0.7898 (0.7532; 0.8265)	4.6%
without peripheral	0.7274 (0.6867; 0.7681)	25.2%
without others	0.7680 (0.7298; 0.8061)	11.8%

Risk factors included in the full model:

- *Central:* Widespread pain; Hospital Anxiety and Depression Scales; Pain Catastrophizing Scale.

- *Peripheral*: History of significant injury; early life mal-alignment; current mal-alignment; high risk occupation; radiographic severity according to the Nottingham LLDA; synovial hypertrophy in mm.
- *Others*: Age; gender; BMI; number of comorbidities; nodal hand osteoarthritis.

Note: AUC – area under the curve; CI –confidence interval.

* $PRC = \frac{AUC_{full} - AUC_{partial}}{AUC_{full} - 0.5}$, where AUC_{full} is AUC for the full risk factor model and $AUC_{partial}$ is AUC for the partial model without an exposure of interest.

3.5.3. Stratified analysis by presence/absence of radiographic OA and widespread pain

Stratified analysis was undertaken to explore whether the association between synovial changes detected on US and knee pain is modified by the presence or absence of WSP as a marker of centrally-mediated symptoms and by the presence or absence of ROA (Table 3-23). The clinical and demographic characteristics of the study subgroups are shown in Appendix 13.

The association between effusion and knee pain was significant only in participants with ROA (aORs for those with and without WSP 7.14, 95% CI 3.03 to 16.83 and 9.01, 95% CI, 4.57 to 17.75, respectively). The association between synovial hypertrophy and knee pain was significant in participants with ROA (aORs for those with and without WSP 7.24, 95% CI 3.04 to 17.25, and 9.99, 95% CI 5.06 to 19.73, respectively) and in those without ROA and without WSP (aOR 2.25, 95% CI 1.19 to 4.22).

Table 3-23. Association between peripheral risk factors and knee pain stratified by ROA and WSP

	Controls (KP- ROA ¹ - WSP ² -)	Subgroup 1 (KP+ ROA+ WSP+)	Subgroup 2 (KP+ ROA+ WSP-)	Subgroup 3 (KP+ ROA- WSP+)	Subgroup 4 (KP+ ROA- WSP-)
N	160	58	116	108	236
Effusion					
<i>mean in mm (SD)</i>	3.87 (2.60)	7.31 (4.39)	7.71 (3.79)	3.86 (2.83)	4.22 (3.10)
<i>≥4mm</i>	62 (38.75)	45 (77.59)	96 (83.48)	40 (37.04)	104 (44.44)
<i>≥4mm OR (95%CI)</i>		5.47 (2.73; 10.95)	7.99 (4.44; 14.35)	0.93 (0.56; 1.54)	1.26 (0.84; 1.90)
<i>≥4mm aOR (95%CI)</i>		7.14 (3.03; 16.83)	9.01 (4.57; 17.75)	0.96 (0.54; 1.69)	1.51 (0.97; 2.35)
Synovial hypertrophy					
<i>mean in mm (SD)</i>	1.26 (2.03)	3.98 (3.10)	4.58 (3.31)	1.58 (2.36)	1.75 (2.50)
<i>≥4mm</i>	17 (10.63)	26 (44.83)	66 (57.39)	21 (19.44)	46 (19.66)
<i>≥4mm OR (95%CI)</i>		6.83 (3.32; 14.06)	11.33 (6.07; 21.15)	2.03 (1.02; 4.06)	2.06 (1.13; 3.74)
<i>≥4mm aOR (95%CI)</i>		7.24 (3.04; 17.25)	9.99 (5.06; 19.73)	2.21 (0.99; 4.93)	2.25 (1.19; 4.22)
Power Doppler					
<i>n (%)</i>	2 (1.25)	2 (3.45)	6 (5.17)	2 (1.85)	6 (2.54)
<i>OR (95%CI)</i>		2.82 (0.39; 20.49)	4.30 (0.85; 21.71)	1.49 (0.21; 10.75)	2.06 (0.41; 10.32)
<i>aOR (95%CI)</i>		6.10 (0.77; 48.62)	4.89 (0.92; 25.98)	2.64 (0.32; 22.07)	2.78 (0.54; 14.28)

Note: Significant associations are highlighted in bold.

aOR – odds ratio adjusted with age, gender, BMI; SD – standard deviation; CI – confidence interval; KP – knee pain.

¹ Widespread pain defined as concurrent pain experienced within the past 4 weeks axially, above and below the waist, and on both sides of the body (ACR criteria) self-reported using a diagrammatic manikin.

² Radiographic osteoarthritis defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

3.5.4. Within-person analysis

Further analysis was undertaken in people with unilateral knee pain (n=242). As can be seen in Table 3-24, US effusion and synovial hypertrophy, PDS, global radiographic score, and ROA were related to pain in this analysis. After adjustment for radiographic severity the association with knee pain remained significant for both effusion and synovial hypertrophy on a continuous scale only. Similarly, after adjustment for synovial hypertrophy the association with knee pain remained significant for global radiographic score on a continuous scale. When people with unilateral knee pain were sub-grouped by the presence or absence of ROA, effusion associated with knee pain in those with ROA only (OR 3.70, 95% CI 1.73 to 7.94, for effusion ≥ 4 mm), whereas synovial hypertrophy associated with knee pain in both subgroups with and without ROA (ORs 2.40, 95% CI 1.23 to 4.69, and 2.09, 95% CI 1.05 to 4.18, respectively).

Table 3-24. Association between peripheral risk factors and knee pain in people with unilateral pain: within person analysis

	Crude		Adjusted	
	OR (95CI)	p-value	aOR (95CI)	p-value
Ultrasound values				
<i>Effusion in mm*</i>	1.12 (1.06; 1.19)	0.0001	1.09 (1.02; 1.16)¹	0.0107
<i>Effusion >=4 mm*</i>	1.55 (1.07; 2.23)	0.0200	1.24 (0.84; 1.83) ¹	0.2763
<i>Synovial thickness in mm*</i>	1.13 (1.06; 1.22)	0.0006	1.08 (1.00; 1.17)¹	0.0445
<i>Synovial thickness >=4 mm*</i>	1.99 (1.28; 3.10)	0.0024	1.52 (0.94; 2.47) ¹	0.0888
<i>Power Doppler Signal*</i>	14.12 (1.81; 109.9)	0.0116	12.52 (1.60; 98.21)¹	0.0163
Radiographic severity				
<i>Global radiographic score (range 0-60)**</i>	1.05 (1.02; 1.08)	0.0005	1.04 (1.00; 1.07)²	0.0275
<i>ROA*</i>	1.82 (1.19; 2.77)	0.0054	1.44 (0.91; 2.29) ²	0.1234

Note: Significant associations are highlighted in bold.

OR – odds ratio; CI – confidence interval; ROA – radiographic osteoarthritis.

¹ adjusted for global radiographic score.

² adjusted for synovial hypertrophy in mm.

Table 3-25. Association between synovial changes detected on US and knee pain in people with unilateral pain: within person analysis stratified by ROA

	OR (95CI)	
	ROA+ (n=77)	ROA- (n=161)
<i>Effusion in mm</i>	1.26 (1.13; 1.39)	1.06 (0.97; 1.16)
<i>Effusion >=4 mm</i>	3.70 (1.73; 7.94)	1.13 (0.72; 1.79)
<i>Synovial thickness in mm</i>	1.18 (1.05; 1.32)	1.15 (1.03; 1.28)
<i>Synovial thickness >=4 mm</i>	2.40 (1.23; 4.69)	2.09 (1.05; 4.18)
<i>Power Doppler Signal</i>	8.55 (1.01; 72.04)	n/a

Note: Significant associations are highlighted in bold.

OR – odds ratio; CI – confidence interval; ROA – radiographic osteoarthritis.

3.5.5. Summary

This study explored the role of peripheral risk factors, including synovial changes detected on US, central and other risk factors that may influence knee pain experience. We found that a number of local, central and other risk factors were associated with knee pain but of these, WSP, pain catastrophising, knee injury, ROA, and synovial changes detected by US showed the strongest association. We also found that the presence of WSP and ROA influenced the association between synovial changes detected on US and knee pain. For example, both effusion and synovial hypertrophy strongly associated with knee pain in participants with ROA regardless of presence/absence of WSP, whereas only hypertrophy associated with knee pain in people without ROA and WSP. This suggests that the contribution from synovial changes detected on US is different between people with knee pain only and those with knee pain plus ROA. These findings were also confirmed by the within-person analysis which fully balances the central and other person-level risk factors. The association with knee pain was confirmed for all three synovial changes detected on US in those with ROA, but for synovial hypertrophy only in those without ROA.

4. DISCUSSION

This chapter aims to: summarise the key findings of this thesis; interpret these findings in the light of previous literature; suggest potential clinical implications of the findings; discuss the caveats of the studies undertaken; and suggest future research questions.

4.1. Key findings, interpretation and caveats

4.1.1. Systematic review

This is the first meta-analysis of US detected synovial changes in people with and without knee OA/pain. Twenty-nine observational studies including 4720 participants from different countries were included in this study. The main findings are: [1] the prevalence of US detected effusion, synovial hypertrophy and positive DS are 2 to 3 times higher in people with knee OA/pain than in the general population or asymptomatic control groups; and [2] the US abnormalities relate more to presence of OA structural change than to pain.

People with knee OA had significantly higher prevalence of effusion, synovial hypertrophy and DS than people with knee pain ($p=0.037$, $p=0.010$ and $p=0.009$, respectively) (Table 3-4). This may be contrary to general expectation since the three US features selected are widely considered to reflect inflammation, and pain in knee OA is suggested to associate with inflammation (Filippucci et al., 2013, Joshua et al., 2007). Importantly, however, this finding suggests that US detected synovial

changes (effusion, hypertrophy, DS) may mainly correlate with the degree of OA structural change and pathology, which increasingly is recognised to involve all tissues that comprise the joint, rather than representing a biomarker/mechanism that links strongly with pain production.

There was significant heterogeneity between studies with respect to prevalence of all three US features. Such heterogeneity is to be expected because a systematic review brings together studies that are diverse both clinically and methodologically (e.g. thresholds of abnormality, recruitment source, sample size, age, gender proportion, BMI, disease duration and definition of knee OA/pain). For example, among studies in people with knee OA/pain the subgroup analysis revealed that studies with quality scores lower than 50% of maximum presented significantly higher prevalence of DS ($p < 0.0001$), and studies with sample size less than 100 reported significantly higher prevalence of effusion and synovial hypertrophy ($p = 0.034$ and $p = 0.015$, respectively). This suggests that small studies tend to inflate the results – the small study effect (Harbord et al., 2006, Harbord et al., 2009). Care must be taken when interpreting the results from such studies as they may overestimate the prevalence of abnormalities.

The second research question was to determine relationships between synovial changes detected on US and knee pain. The majority of studies reported a positive association between presence of effusion and knee pain (7 out of 10) but no association between synovial hypertrophy and

pain (2 out of 6) (Table 3-6). US-detected findings were also associated with structural changes on radiographs in two of the three studies (D'Agostino et al., 2005, Wu et al., 2012, Hall et al., 2014). However, our subgroup analysis according to knee pain and knee OA suggests that these three US abnormalities relate more to knee OA (either ACR symptomatic or radiographic) than to knee pain. Further study is required to explain this finding.

A paucity of information was found on the prevalence of synovial changes detected on US in the general population and no prospective community studies were identified. Considering gender differences and possible associations between normal values and changes in the musculoskeletal system and body composition with increasing age, knowledge of the normal values of synovial changes detected on US would seem essential for the classification and diagnosis of people with knee pain and OA. It is expected that the normal values for older adults might differ from those for younger people, since age-related changes contribute to alterations in cartilage morphology, proprioception and muscle weakness even in the absence of OA. For example, in the Framingham study the prevalence of effusion/synovitis on MRI in people without knee OA was 37% if the present/absent scale was applied but only 4% if defined by WOMBS grade two or more. Such synovitis was detected significantly more often in men than women (6% and 3%, respectively; $p=0.02$), but there was no difference in relation to presence of knee pain or BMI (Guermazi et al., 2012). However, at present the characteristics of

synovial changes detected on US especially in older age groups remains unknown.

There are several limitations to this study. Firstly, we focused only on the knee, so the results cannot be extrapolated to other joints. Secondly, there was significant heterogeneity in the results on prevalence, so the results of this review need to be interpreted with caution. For example, differences in scanning technique were common within included studies (e.g. neutral versus flexed knee position, multi-planar versus midline scan (Appendix 9)) which might affect the results and together with differences in participant characteristics (age, gender, disease duration, severity of structural changes) might explain some of the between-study heterogeneity (Terslev et al., 2012, Song et al., 2009, Zivanovic et al., 2009a). Thirdly, the prevalence in the general population was obtained from just a few studies including controls from case control studies. This group was neither a random sample of the general population, nor comparable to the cases with knee OA/pain. The prevalence obtained from such an assembled “normal” control group cannot be extrapolated to the prevalence in the general population.

This study highlights the lack of information on the presence of synovial change in the knee. Although many studies have explored this question, none has investigated the distribution of these features in the general population, hence the threshold for abnormality has yet to be established. US-detected pathology should be described in detail and studies should provide sufficient information on definition and thresholds used. The

heterogeneity across studies highlights the need for a standard protocol in order to allow comparability between studies in the future.

In conclusion, US detected effusion, synovial hypertrophy and DS are more common in people with knee OA/pain, compared to the general population. These abnormalities appear to relate more to presence of OA structural changes than to pain. Further studies to examine the reasons for this difference and to determine normal values of the US features and their thresholds for abnormality are warranted.

4.1.2. Reproducibility

The reliability of both US assessment and radiographic scoring was an important issue to consider prior to conducting the studies presented in this thesis. For US, the reliability exercise demonstrated the moderate to good intra- and inter-rater agreement in the detection of synovial changes. The level of agreement between observers was moderate for effusion and substantial for synovial hypertrophy (kappa 0.44 and 0.61, respectively). Intra-observer agreement for effusion was moderate (kappa 0.50). There were insufficient data to calculate kappa statistics for synovial hypertrophy (concordance correlation coefficient 0.84, mean difference between measurements 0.3 mm, SD 0.7) and PDS.

The achieved level of agreement is comparable with results of an OMERACT reliability exercise in knee OA participants (Bruyn et al., 2016). In that study the agreement between 11 experienced sonographers was fair for both effusion and synovial hypertrophy (mean

kappa statistics 0.38 and 0.29, respectively) and the intra-rater agreement was moderate for both US features (mean kappa statistics 0.56 and 0.49, respectively) (Bruyn et al., 2016).

Substantial inter-observer and intra-observer agreement was demonstrated for the radiographic scoring (all kappa values >0.78). The reproducibility of radiographic assessment according to the NLDA achieved in our study is in line with other studies (Nagaosa et al., 2000, Wilkinson et al., 2005). In these two studies the reported inter-rater kappa-statistics ranged from 0.47 to 0.79 for osteophytes grading, and from 0.65 to 0.86 for JSN grading. In our study the agreement was similar (kappa 0.68 and 0.69, respectively). Intra-rater agreement was reported only in one study as kappa 0.68 for osteophytes and 0.82 for JSN. In addition, in this study we defined presence of ROA as definite JSN (grade >2) and definite osteophyte (grade >2) in any compartment (tibiofemoral or patellofemoral) using the NLDA, and definite osteophyte and definite JSN (grade ≥ 3) using the K&L scale. The reproducibility of this definition reached a substantial level (kappa 0.78) in the inter-rater test and an excellent level (kappa 1.0) in intra-rater assessments.

Overall, in our reliability study inter- and intra-rater reliability was at a satisfactory level for both US and radiographic assessments.

4.1.3. Thresholds of synovial changes detected on US for knee osteoarthritis – a cross sectional study in the general population

To our knowledge the study presented in Section 3.3 is the first population-based study in an age-range suitable for knee OA to investigate reference values for effusion and synovial hypertrophy and the optimal cut-off for identification of knee pain and ROA. The main findings of this study are: [1] synovial changes detected on US are different between men and women, therefore, gender-specific reference limits should be applied; [2] the upper reference limit for effusion is 10.3 mm for men and 9.8 mm for women and the upper reference limit for synovial hypertrophy is 6.8 mm for men and 5.4 mm for women; and [3] the effusion cut-off with high specificity for a subgroup of people with knee pain and ROA (i.e. “symptomatic OA”) is 8.9 mm for men and 7.8 mm for women, and for synovial hypertrophy it is 5.8 mm for men and 4.2 mm for women.

In this study the normal values for effusion and synovial hypertrophy detected by US were established in a random sample of the general population older than 40 years. No previous studies have reported reference values for US in the whole general population aged 40 years upwards. Recently a large study of D'Agostino et al. (2015) reported a high prevalence of US-detected changes in a population-based cohort aged >60 years old (effusion present in 69.7% and synovial hypertrophy in 53.1%). However, no data on distribution (mean values, minimum-maximum range) were reported. Nevertheless, the high prevalence of US features in this cohort is in line with our results. The reference values

were established for men and women separately as we found significantly higher values of effusion and synovial hypertrophy in men compared to women. The subgroup-based reference ranges provide more sensitive and specific results and improved clinical application (Harris and Boyd, 1990). Our results are in line with the study of D'Agostino et al. (2005) that reported that women had fewer joint effusions than men (OR 0.62).

In our study the prevalence of PDS was very low in people without knee pain and ROA (1% in men and 0% in women) and in the general population regardless of knee pain and ROA (in right knees 5.3% in men and 0.68% in women, $p=0.0204$; in left knees 2.63% and 0.68% respectively, $p=0.1883$). Two studies previously reported prevalence of PDS in the general population (D'Agostino et al., 2015, Hall et al., 2014). In the study by Hall et al. (2014) the prevalence of PDS in pain-free people without ROA ($n=90$) was 2.2%, which is in line with our findings. In the study by D'Agostino et al. (2015) the prevalence of PDS was 31.8%. However, this cohort ($n=433$) was older (range 60-98) and the prevalence of knee pain was 31.6%.

The second objective was to determine a cut-off (decision limit) to decide on a specific level of probability for the presence of a knee abnormality (knee pain plus ROA). It is important to recognise the difference between the reference intervals and decision limit (cut-off). The reference interval is the range of values that would reflect the biological variability of a diagnostic marker in a "healthy" population. Typically, reference intervals

are referred to as normal values and therefore any test result would be interpreted relative to its upper (or lower) limit. However, for many diagnostic tests normal values have been defined on the basis of analysis of clinical outcomes (Boyd, 2010). So-called decision limits depend on the type of pathological condition being examined and the type of decision to be made (Ceriotti and Henny, 2008). For example, the 97.5 percentile for cholesterol concentration in the general population lies between 280 and 300 mg dL⁻¹ (7.25–7.77 mmol L⁻¹), while the decision thresholds associated with moderate and high risks for the development of cardiovascular disease are 200 mg dL⁻¹ (5.18 mmol L⁻¹), and 240 mg dL⁻¹ (6.22 mmol L⁻¹), respectively (National Cholesterol Education Program (NCEP) Expert Panel, (2001)). Therefore, in this study in addition to the reference intervals for effusion and hypertrophy in pain-free participants without ROA, we calculated cut-offs corresponding to the presence of knee pain plus ROA (decision limit). Because of the large overlap between people with and without knee pain and ROA, we applied two different methods to establish a decision limit. Firstly, we calculated an optimal cut-off using the Youden Index. This method has been used widely to identify an optimal cut-off with maximum sensitivity and specificity (Perkins and Schisterman, 2006, Subtil and Rabilloud, 2014). Secondly, we calculated a threshold corresponding to a pre-defined specificity of 90% to identify a subgroup of people with knee pain and ROA who are different from the healthy population. These cut-offs corresponded with the highest likelihood ratio of a positive test result

("LR+" \approx 5). This subgroup is more likely to represent an "inflammatory" phenotype.

There are several limitations to this study. Firstly, KPIC is a questionnaire-based cohort study, therefore participants with knee pain may be more likely to respond to the baseline and follow-up questionnaire and agree to receive information about other projects (response bias). Secondly, sampling bias cannot be discounted. Although we randomly selected participants for this study from the KPIC cohort, people with knee pain are generally more willing to participate in a clinical assessment (prevalence of current knee pain was 21% in non-responders and 30% in responders, $p=0.036$). The sampling bias also could account for the unrepresentativeness of the younger age group (less than 55) as the working age population is less likely to respond to the invitation. Thirdly, we used "current knee pain" definition to divide our sample into those with and without knee pain in order to determine the decision threshold for both US values. Previous studies showed that this question recommended by the American College of Rheumatology (ACR) as a criteria for knee OA is the most specific (72.7%) but least sensitive (45.4%) in relation to osteophytes (grade ≥ 1) and as a predictor of disability due to knee pain (O'Reilly et al., 1996). However, applying a different knee pain definition may lead to a different decision threshold. Fourthly, pain and US features were measured at one time point only and longer follow-up might have allowed better discrimination and predictive value. Furthermore, this is a single-centre study of the community in

Nottinghamshire. Therefore, community-based studies in different geographical areas or in different countries may show different results.

In summary, this study suggests that effusion and synovial hypertrophy but not PDS are common findings in the general population and in people without knee pain and ROA. Different thresholds for both effusion and synovial hypertrophy should be applied for men and women. In order to identify a subgroup of people with knee pain plus ROA who are different from the healthy population a decision threshold corresponding with a high specificity is recommended.

4.1.4. Association between synovial changes detected on US and knee pain: a population-based case-control study with both cross-sectional and follow-up data

To our knowledge, this is the first community-based study to investigate synovial changes detected on US and their association with knee pain, adjusted for ROA, in the earlier and later stages of the condition. The main findings are: [1] synovial changes detected on US associate with knee pain, but the association is confounded by ROA severity; [2] changes in effusion or synovial hypertrophy do not correlate with changes in knee pain over one-year; [3] effusion and ROA severity but not synovial hypertrophy at baseline predict knee pain worsening at one-year.

Our findings suggest that the association between synovial changes detected on US (“synovitis”) and knee pain may be confounded by radiographic structural changes of OA. This is supported by: [1] the strong dose-response association between ROA and synovial hypertrophy; [2] the diminishing association between knee pain and effusion after adjustment for ROA; [3] the lack of correlation between change in knee pain and change in any US synovial feature; and [4] the inconsistent prediction of synovial changes detected on US (effusion but not synovial hypertrophy) for pain worsening in contrast to the prediction of baseline ROA change for pain worsening in one year. This suggests that “synovitis” detected by US may not be the main cause of knee pain but a consequence of the overall pathology of OA that involves all joint tissues. This has been confirmed by the graded ORs from no knee pain, to early knee pain and then to established knee pain (Table 3-15). The

gradual increase in effusion and synovial hypertrophy over one year is also more likely to be an integral part of attempted repair and structural remodelling of the “whole joint”. This view is supported by the strong association demonstrated between synovial changes detected on US and radiographic severity (Figure 3-13, Figure 3-15). This begs the question as to whether there is any causality between structural damage and inflammation and whether OA is a disease driven by inflammation or a condition that includes some structure-related inflammation as part of the joint insult/remodelling process. We therefore undertook an analysis to examine whether radiographic baseline score was a predictor for change in US synovial score but this showed no association between the two. Further studies that specifically examine the relationship between synovial change and change in other joint tissues are warranted.

The association between synovial changes and knee pain have been investigated previously. In our meta-analysis (Section 3.1) seven out of ten studies reported a positive association between KP and effusion and two out of six reported an association with synovial hypertrophy. However, most studies did not adjust for ROA. Although the prevalence of US-detected synovial pathology (effusion, hypertrophy, PD) showed wide variability between studies, the pooled prevalence of these features was significantly higher in people with knee OA than in people with knee pain ($p < 0.05$). This prompted the current study to investigate the relationship between US features of “synovitis”, ROA and knee pain. Our conclusion is that both US “synovitis” and ROA are risk factors for knee pain and strongly relate to each other. The positive association between

synovial changes and structural severity accords with MRI findings (Wang et al., 2016b, Hunter et al., 2013). This explains why the association between KP and synovial changes reduced after adjusting for radiographic severity or vice versa.

In accord with our findings, Hall et al. (2014) found no association between changes in knee pain and changes in US features over 3 months. The evidence supporting the link between changes in pain and MRI-detected synovitis are limited and controversial. For example, changes in synovitis associated with fluctuations in knee pain in the Multicentre OA Study over 30 months (Zhang et al., 2011b). However, synovitis changes detected on contrast-enhanced MRI were not associated with changes in pain over a 2-year period in a more recent study by de Lange-Brokaar et al. (2016).

In our study we found that presence of ROA is a prognostic factor that predicts worsening of pain over 1 year. The association between structural severity and knee pain has been confirmed in a number of cross-sectional studies (Neogi et al., 2009) whereas evidence for ROA as a predictor of knee pain progression remained controversial (de Rooij et al., 2016, Wesseling et al., 2015)

Recently, there has been considerable interest in inflammation in OA and the possibility that “synovitis” is a marker for an inflammatory phenotype of symptomatic OA (Sokolove and Lepus, 2013, Berenbaum, 2013). However, in contrast to RA and other arthropathies that are driven by inflammation, the intensity of inflammation in OA is only modest. Early

morning and inactivity stiffness are relatively short in OA (Altman et al., 1986) and large effusions are atypical and suggest co-existing inflammatory conditions such as crystal synovitis (Ledingham et al., 1995, Rosenthal, 2011, Ramonda et al., 2014). Furthermore, although synovial hyperplasia and effusion may occur in OA, synovial hyperplasia is more focal than generalised, effusions have relatively low cell counts with preponderance of mononuclear cells, and marginal cortical erosions do not occur (Pritzker, 2003, Brandt et al., 2008). This contrasts with RA where high cell counts (causing turbidity) with predominance of neutrophils, and development of marginal cortical erosions are characteristic. It is possible that effusion in knee OA in part is non-inflammatory, arising from attrition of lymphatics rather than fluid overproduction due to inflammation (Walsh et al., 2012). Generalised synovial hypertrophy and strongly positive PDS are US markers of inflammation in RA (Schmidt et al., 2015, Naredo and Iagnocco, 2016), the PDS indicating marked hypervascularity, a central aspect of florid inflammation. Although we found a positive association between synovial hypertrophy and knee pain the prevalence of PDS was very low in both knee pain groups. Therefore, our data align with the perspective of OA as an inherent repair process in which all tissues that comprise the synovial joint, including the synovium and capsule, respond to diverse insults (including biomechanical factors) by producing new tissue (Pritzker, 2003).

There are several caveats to this study. Firstly, it was designed primarily to determine the association between synovial changes detected on US

and knee pain so other associations should be interpreted with caution. It is possible that the associations between US and ROA with knee pain might result from other associated factors. Secondly, the overall rate of worsening of knee pain in our population, especially in people with established knee pain (42%) was higher than in previous knee pain studies (19% in a study of Jinks et al. (2008)). This may reflect response bias in that people with KP generally are more likely to respond to a questionnaire on KP. However, we could not find any meaningful difference in baseline characteristics between responders and the source population (Table 2-5). Thirdly, pain and US features were measured at just two time points and further longer-term follow-up is desirable. Fourthly, currently there is no accepted standardised protocol for US assessment. Our study included assessment of three areas (suprapatellar pouch, medial and lateral aspects of the knee) with the maximum value of effusion/hypertrophy recorded per knee. Previously Karim et al. (2004) reported that these three areas have similar sensitivity for detection of synovitis compared with synovitis detected using arthroscopy (gold standard) (Karim et al., 2004). However, a more detailed protocol with separate scoring per area or using multi-compartmental summated score might reveal different associations with knee pain. Fifthly, US and radiographs cannot examine all joint changes in OA (e.g. bone marrow lesions) and use of MRI, although expensive, would have allowed more detailed and comprehensive assessment of joint abnormalities. Finally, the reliability of US assessment is an important issue to consider. The level of agreement between observers

was not perfect but at least moderate and in line with an OMERACT reliability exercise (Bruyn et al., 2016).

In summary, synovial changes detected on US associate with knee pain but the association is confounded by structural OA. While effusion and structural OA predict worsening of knee pain over a one year period, changes in effusion or synovial hypertrophy do not correspond to change in knee pain. Synovial changes detected on US are related to radiographic severity of OA but the causal relationship between the two has yet to be established.

4.1.5. Contribution of central vs peripheral risk factors (including synovial changes on ultrasound) to knee pain

This is the first population-based study to investigate the contribution of both central and peripheral risk factors to knee pain in the same study, and to examine the association between synovial changes detected on US and knee pain in the presence or absence of WSP and ROA. The main findings are: [1] a number of both local and systemic risk factors associate with knee pain, including WSP, pain catastrophising, knee injury, ROA, effusion and synovial hypertrophy; [2] effusion associates with knee pain in people with ROA only, whereas synovial hypertrophy associates with knee pain in people with ROA (regardless of WSP) and without ROA (without WSP only).

In the present study we examined multiple risk factors relating both to local joint pathophysiology (US features, ROA) and to central pain modulation (WSP, anxiety, depression, catastrophizing). Our findings confirmed that many of these associate with knee pain (Table 3-21). These findings are in line with previous studies that report an association between knee pain/OA and WSP, depression, high-risk occupation, ROA and synovial changes detected on US (Silverwood et al., 2015, Blagojevic et al., 2010, Sarmanova et al., 2016). Furthermore, the relative contribution of risk factors to knee pain was estimated in one model. This showed that risk factors related to structural severity contributed more to knee pain than risk factors related to central pain processing (25% vs 5%, Table 3-22).

While a number of risk factors are involved in KP, we were interested particularly in how WSP, as a marker of centrally mediated symptoms, and ROA, as evidence of structural severity, influence the association between synovial changes detected on US and knee pain. For this purpose, we conducted two analyses. Firstly, we looked at the association between effusion, synovial hypertrophy and DS and knee pain in subgroups stratified by the presence/absence of WSP and ROA. In people with ROA synovial changes on US were associated with knee pain regardless of WSP, whereas in people without ROA only synovial hypertrophy was associated with knee pain in the absence of WSP (Table 3-23). Secondly, we looked at the association between synovial changes detected on US and knee pain in people with unilateral pain. This design has the advantage of perfectly controlling person-specific central and systemic features in the between-knee comparison and the results are in line with the main results on the dependency between peripheral risk factors and knee pain (Table 3-25). This analysis confirmed that when the central risk factors are fully balanced both effusion and hypertrophy are associated with knee pain in people with ROA, but only hypertrophy is associated with knee pain in people without ROA.

These findings suggest that synovial changes detected on US contribute to knee pain but the presence of ROA significantly affects this association, supporting the view that knee pain is a common complex condition that involves multiple causal pathways. Moreover, effusion may be related to structural severity more than synovial hypertrophy. Firstly, when we sub-grouped people by ROA (cross-sectionally and in within-

person analysis) effusion associated with knee pain in those with ROA only. Secondly, in our case-control study (Section 3-4) the association between effusion and knee pain diminished after adjustment for the global radiographic score, whereas the association between hypertrophy and knee pain decreased but remained significant after adjustment. Thirdly, in our longitudinal analysis both effusion and ROA predicted worsening of knee pain while synovial hypertrophy did not.

Interestingly, synovial changes detected on US were not associated with knee pain in people without ROA but with WSP (Table 3-23). This finding is in line with the few studies that have examined the association between central and peripheral risk factors and knee pain. Riddle and Stratford (2014) reported that people with high levels of pain and low knee ROA grades (K&L 1-2) are more likely to have WSP compared to those with low pain and high ROA grades (relative risk (RR) 2.3, 95% CI 1.6 to 3.3). Finan et al. (2013) also confirmed that people with high levels of pain and low knee ROA grades (K&L 1-2) show higher pain sensitivity on QST compared to those with low pain and high ROA grades. Pereira et al. (2013) showed that the association between knee pain and ROA (K&L grade ≥ 2) is stronger in people without depressive symptoms. This suggests that in people with predominantly centrally-mediated symptoms the contribution of peripheral damage to knee pain is less.

There are several caveats to this study. Firstly, the stratified analysis by presence/absence of WSP and ROA and within-person analysis should be interpreted with caution because of a possible “small study” effect

(Christley, 2010, Nüesch et al., 2010) and further studies with sufficient power are required. Secondly, the within-participant control study could have been biased by possible biomechanical adaptation of the contralateral joint (Messier et al., 2016) and the fact that people with unilateral KP are more likely to develop incident disease in the contralateral knee (Wenham et al., 2012, Felson et al., 1995). Therefore the observed changes in contralateral knees could be an early marker of developing OA (Sutton et al., 1997).

In conclusion, this study confirms that many central and peripheral risk factors associate with knee pain. Synovial changes detected on US contribute significantly to knee pain, but the presence of centrally-mediated symptoms and ROA influences this association. Further study of the causality between peripheral and central risk factors is needed.

4.2. Conclusion and future work

In summary, key findings from the studies undertaken for this thesis are as follows:

1. Effusion and synovial hypertrophy but not PDS are common findings in the general population and in people without knee pain and ROA.
1. There is a marked gender difference in these two synovial changes detected on US. Therefore, we propose that different thresholds for both effusion and synovial hypertrophy should be applied in men and women.
2. In order to identify a subgroup of people with knee pain and ROA (“symptomatic knee OA”) different from the healthy population a decision threshold corresponding with high specificity is recommended.
3. Synovial changes detected on US are associated with knee pain but the association depends on the type of knee pain. If knee pain is mainly caused by peripheral risk factors (such as structural radiographic changes), both effusion and hypertrophy associate with it. However, if knee pain is mainly caused by central risk factors in the absence of ROA synovial changes detected on US do not associate with it.
4. The changes in effusion or synovial hypertrophy did not correspond to a change in knee pain, but baseline effusion predicted worsening of knee pain in one year.

5. Synovial changes detected on US are related to radiographic severity of OA but the causal relationship between the two are unclear.

Further research is still required to confirm the importance of synovial changes detected on US as a primary outcome to gauge clinical response or to guide clinical decisions. Firstly, the causal relationships between US changes, ROA and knee pain, and the influence of central pain modulation deserves further study. Ideally this requires population-based prospective studies of incident KP and of incident/early structural knee OA (using MRI) to determine the role of synovial changes detected on US in risk of pain and pain outcomes. Secondly, despite the lack of association between synovial changes detected on US and changes in knee pain after one year, the prognostic value of US remains uncertain in people with OA. Longer follow-up studies are required to explore the longitudinal associations between the synovial changes detected on US and changes in knee pain. Thirdly, a standardised protocol for US assessment of the knee joint is necessary. It is important to determine whether synovial changes detected on US differ between compartments in their association with structural severity and contribution to knee pain.

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APPENDIX 1 SEARCH STRATEGY FOR SYSTEMATIC LITERATURE REVIEW

Database	Search strategy	Articles identified
	Systematic search I (December 2014):	
Ovid MEDLINE	<p>1 knee osteoarthritis.mp. or exp Knee Osteoarthritis/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>2 knee osteoarthrosis.mp.</p> <p>3 (gonarthritis or gonarthrosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>4 knee pain.mp. or exp Knee Pain/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>5 osteoarthritis.mp. or exp OSTEOARTHRITIS/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>6 osteoarthrosis.mp.</p> <p>7 osteophyte.mp. or exp OSTEOPHYTE/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>8 joint space narrowing.mp.</p> <p>9 degenerative joint disease\$.mp.</p> <p>10 5 or 6 or 7 or 8 or 9</p> <p>11 knee.mp. or exp KNEE/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>12 10 and 11</p> <p>13 1 or 2 or 3 or 4 or 12</p> <p>14 ultrasound.mp.</p> <p>15 sonography.mp. or exp ultrasonography/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>16 doppler.mp. or exp dopplerography/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>17 Ultrasonography, Doppler, Color/ or Ultrasonography, Doppler/ or powerdoppler. mp.</p> <p>18 14 or 15 or 16 or 17</p> <p>19 13 and 18</p> <p>20 limit 19 to humans</p>	323
Embase	<p>1 knee osteoarthritis.mp. or exp Knee Osteoarthritis/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>2 knee osteoarthrosis.mp.</p> <p>3 (gonarthritis or gonarthrosis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>4 knee pain.mp. or exp Knee Pain/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>5 osteoarthritis.mp. or exp OSTEOARTHRITIS/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>6 osteoarthrosis.mp.</p>	1317

	<p>7 osteophyte.mp. or exp OSTEOPHYTE/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>8 joint space narrowing.mp.</p> <p>9 degenerative joint disease\$.mp.</p> <p>10 5 or 6 or 7 or 8 or 9</p> <p>11 knee.mp. or exp KNEE/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>12 10 and 11</p> <p>13 1 or 2 or 3 or 4 or 12</p> <p>14 ultrasound.mp.</p> <p>15 sonography.mp. or exp ultrasonography/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>16 doppler.mp. or exp dopplerography/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]</p> <p>17 Ultrasonography, Doppler, Color/ or Ultrasonography, Doppler/ or powerdoppler. mp.</p> <p>18 14 or 15 or 16 or 17</p> <p>19 13 and 18</p> <p>20 limit 19 to humans</p>	
AMED	<p>1 knee osteoarthritis.mp. or exp Knee Osteoarthritis/ [mp=abstract, heading words, title]</p> <p>2 knee osteoarthrosis.mp.</p> <p>3 (gonarthrosis or gonarthrosis).mp. [mp=abstract, heading words, title]</p> <p>4 knee pain.mp. or exp Knee Pain/ [mp=abstract, heading words, title]</p> <p>5 osteoarthritis.mp. or exp OSTEOARTHRITIS/ [mp=abstract, heading words, title]</p> <p>6 osteoarthrosis.mp.</p> <p>7 osteophyte.mp. or exp OSTEOPHYTE/ [mp=abstract, heading words, title]</p> <p>8 joint space narrowing.mp.</p> <p>9 degenerative joint disease\$.mp.</p> <p>10 5 or 6 or 7 or 8 or 9</p> <p>11 knee.mp. or exp KNEE/ [mp=abstract, heading words, title]</p> <p>12 10 and 11</p> <p>13 1 or 2 or 3 or 4 or 12</p> <p>14 ultrasound.mp.</p> <p>15 sonography.mp. or exp ultrasonography/ [mp=abstract, heading words, title]</p> <p>16 doppler.mp. or exp dopplerography/ [mp=abstract, heading words, title]</p> <p>17 Ultrasonography, Doppler, Color/ or Ultrasonography, Doppler/ or powerdoppler. mp.</p> <p>18 14 or 15 or 16 or 17</p> <p>19 13 and 18</p>	31
PubMed	<p>((knee[Title/Abstract] AND (((osteoarthritis[Title/Abstract] OR osteoarthrosis[Title/Abstract]) OR osteophyte\$ [Title/Abstract]) OR joint space narrowing[Title/Abstract]) OR degenerative joint disease\$ [Title/Abstract])) OR (((knee osteoarthritis[Title/Abstract] OR (exp[All Fields] AND ("osteoarthritis, knee"[MeSH Terms] OR ("osteoarthritis"[All Fields] AND "knee"[All Fields]) OR "knee osteoarthritis"[All Fields] OR ("knee"[All Fields] AND "osteoarthritis"[All Fields])))) AND Title/Abstract[All Fields] OR ("osteoarthritis, knee"[MeSH Terms] OR ("osteoarthritis"[All Fields] AND "knee"[All Fields]) OR "knee osteoarthritis"[All Fields] OR ("knee"[All Fields] AND "osteoarthrosis"[All Fields]) OR "knee osteoarthrosis" [All Fields])) AND Title/Abstract[All Fields] OR (gonarthrosis[Title/Abstract] OR ("osteoarthritis, knee"[MeSH Terms] OR ("osteoarthritis"[All Fields] AND "knee"[All Fields]) OR "knee osteoarthritis"[All Fields] OR "gonarthrosis"[All Fields])))) AND Title/Abstract[All Fields] OR (knee pain[Title/Abstract] OR (exp[All Fields] AND ("knee"[MeSH Terms] OR "knee"[All Fields] OR "knee joint"[MeSH Terms] OR ("knee"[All Fields] AND "joint"[All Fields]) OR "knee joint"[All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields]))) AND</p>	200

	Title/Abstract[All Fields]) AND ((ultrasound[Title/Abstract] OR sonography[Title/Abstract] OR ultrasonography [Title/Abstract])	
Scopus	knee osteoarthritis or Knee Osteoarthritis OR knee osteoarthritis OR (gonarthrosis or gonarthrosis) OR knee pain or Knee Pain OR ((osteoarthritis or OSTEOARTHRITIS OR osteoarthritis OR osteophyte or OSTEOPHYTE OR joint space narrowing OR degenerative joint disease) AND knee or KNEE) AND ultrasound OR sonography or ultrasonography OR doppler or dopplerography OR Ultrasonography, Doppler, Color or Ultrasonography, Doppler or power-doppler	1183
Web of science	TITLE-ABS-KEY(((knee osteoarthritis) OR (knee osteoarthritis) OR (gonarthrosis or gonarthrosis) OR (knee pain) OR (((osteoarthritis) OR (osteoarthritis) OR (osteophyte) OR (joint space narrowing) OR (degenerative joint disease\$)) and (knee))) AND ((ultrasound) OR (ultrasonography) OR (doppler) OR (dopplerography) OR (power-doppler) OR (color doppler))) AND (LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"re") OR LIMIT-TO(DOCTYPE,"cp") OR LIMIT-TO(DOCTYPE,"le")) AND (LIMIT-TO(SUBJAREA,"MEDI") OR LIMIT-TO(SUBJAREA,"HEAL")) AND (LIMIT-TO (EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD,"Humans")) AND (EXCLUDE(SUBJAREA,"BIOC") OR EXCLUDE(SUBJAREA,"NEUR") OR EXCLUDE(SUBJAREA,"ENGI") OR EXCLUDE(SUBJAREA,"PHYS") OR EXCLUDE(SUBJAREA,"AGRI"))	1095
	Systematic search II (May 2015):	
Ovid 1 MEDLINE	1 Knee/ 2 knee\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3 ultrasound.mp. 4 Ultrasonography, Doppler, Color/ or sonography.mp. or Ultrasonography/ 5 Ultrasonography, Doppler, Color/ or Ultrasonography, Doppler, Pulsed/ or Ultrasonography, Doppler, Duplex/ or doppler*.mp. or Ultrasonography, Doppler/ 6 normal.mp. 7 healthy.mp. 8 general.mp. 9 population-based.mp. 10 1 or 2 11 3 or 4 or 5 12 6 or 7 or 8 or 9 13 10 and 11 and 12 14 limit 13 to (humans and "all adult (19 plus years)")	409
Embase	1 Knee/ 2 knee\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3 ultrasound.mp. 4 Ultrasonography, Doppler, Color/ or sonography.mp. or Ultrasonography/ 5 Ultrasonography, Doppler, Color/ or Ultrasonography, Doppler, Pulsed/ or Ultrasonography, Doppler, Duplex/ or doppler*.mp. or Ultrasonography, Doppler/ 6 normal.mp. 7 healthy.mp. 8 general.mp. 9 population-based.mp. 10 1 or 2 11 3 or 4 or 5 12 6 or 7 or 8 or 9 13 10 and 11 and 12 14 limit 13 to (humans and "all adult (19 plus years)")	1372

	limit 14 to human	
AMED	<p>1 Knee/</p> <p>2 knee\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]</p> <p>3 ultrasound.mp.</p> <p>4 Ultrasonography, Doppler, Color/ or sonography.mp. or Ultrasonography/</p> <p>5 Ultrasonography, Doppler, Color/ or Ultrasonography, Doppler, Pulsed/ or Ultrasonography, Doppler, Duplex/ or doppler*.mp. or Ultrasonography, Doppler/</p> <p>6 normal.mp.</p> <p>7 healthy.mp.</p> <p>8 general.mp.</p> <p>9 population-based.mp.</p> <p>10 1 or 2</p> <p>11 3 or 4 or 5</p> <p>12 6 or 7 or 8 or 9</p> <p>13 10 and 11 and 12</p> <p>14 limit 13 to (humans and "all adult (19 plus years)")</p> <p>limit 14 to human</p>	34
PubMed	(((knee) OR knee\$)) AND (((((ultrasound) OR sonography) OR ultrasonography) OR doppler) OR dopplerography) OR power-doppler) AND (((healthy) OR general) OR normal) limit to humans	772
Scopus	<p>TITLE-ABS-KEY(("knee" OR "knee\$") AND ("ultrasound" OR "sonography" OR "ultrasonography" OR "doppler" OR "dopplerography" OR "power-doppler") AND ("healthy" OR "general" OR "normal")) limit to human, articles</p> <p>TITLE-ABS-KEY (("knee" OR "knee\$") AND ("ultrasound" OR "sonography" OR "ultrasonography" OR "doppler" OR "dopplerography" OR "power-doppler") AND ("healthy" OR "general" OR "normal")) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re") OR LIMIT-TO (DOCTYPE, "cp") OR LIMIT-TO (DOCTYPE, "ip")) AND (LIMIT-TO (EXACTKEYWORD, "Human"))</p>	863
Web of science	<p># 1 TS=(knee OR knee*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years</p> <p># 2 TS=(ultrasound OR sonography OR ultrasonography OR doppler OR dopplerography OR power-doppler) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years</p> <p># 3 TS=(normal OR healthy OR general OR population-based) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years</p> <p># 4 (#3 AND #2 AND #1) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC Timespan=All years</p>	1029

APPENDIX 2. ETHICAL APPROVAL LETTERS



Health Research Authority

East Midlands - Nottingham 1 Research Ethics Committee

Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839273

19 January 2016

Professor Michael Doherty
Professor of Rheumatology Academic Rheumatology Clinical Sciences Building
Nottingham City Hospital
Nottingham
NG5 1PB

Dear Professor Doherty,

Study title:	Knee synovial changes detected by ultrasound in the general population: cross sectional study
REC reference:	15/EM/0529
Protocol number:	15088
IRAS project ID:	188820

Thank you for your letter of 7th January 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ms Rachel Nelson, NRESCommittee.EastMidlands-Nottingham1@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		06 November 2015
Letter from sponsor		06 November 2015
Letters of invitation to participant	1.1	04 January 2016
Participant consent form	1.1	04 January 2016
Participant information sheet (PIS)	1.1	04 January 2016
REC Application Form [REC_Form_11112015]		11 November 2015
Research protocol or project proposal	1.0	16 October 2015
Summary CV for Chief Investigator (CI)		09 November 2015
Summary CV for student		10 November 2015
Summary CV for supervisor (student research)		10 November 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “*After ethical review – guidance for researchers*” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form

available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at

<http://www.hra.nhs.uk/hra-training/>

15/EM/0529

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely,



**Dr Carl Edwards
Chair**

Email: NRESCCommittee.EastMidlands-Nottingham1@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Angela Shone*

Dr Maria Koufali

Research & Innovation
Nottingham Health Science Partners
C Floor, South Block
Queen's Medical Centre Campus
Derby Road, Nottingham NG7 2UH

12th February 2016

Tel: 0115 9709049
www.nuhrise.org

Professor Michael Doherty
Academic Rheumatology
Clinical Sciences Building
Nottingham City Hospital
Hucknall Road
Nottingham
NG5 8ES

Dear Professor Michael Doherty

Short Title / Acronym	Knee synovial changes detected by ultrasound in the general population /
CSP Number	
R&I REF	15RH015
Long Title	Knee synovial changes detected by ultrasound in the general population: cross sectional study
PROJECT MILESTONES	
Recruitment Target	200
Date of Valid Submission	04/02/2016
Recruitment End Date	15/08/2016
1st Patient to be Recruited by	14/04/2016

The R&I Department has reviewed the following documents and NHS permission for the above research has been granted on the basis described in the application form, protocol, and supporting documentation. The documents reviewed were:

Document	Version	Date
Research protocol	1.0	16 October 2015
Participant information sheet (PIS)	1.1	04 January 2016
Participant consent form	1.1	04 January 2016
Letters of invitation to participant	1.1	04 January 2016

Your study now has NHS permission, on the understanding and provision that you will follow the conditions set out below.

Conditions of Approval

The Principal Investigator is responsible for:

1. Compliance with all relevant laws, regulations and codes of practice applicable to the trial including but not limited to, the UK Clinical Trials Regulations, Medicines for Human Use (Clinical Trial) Regulations 2004, principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2013 version), the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, and the NHS Research Governance Framework for Health and Social Care (version 2 April 2005). Should any of these be revised and reissued this will apply. Copies of the up-to-date regulations are available from the R&I Office or via the R&I website <http://nuhrise.org>.
2. Submission of study amendments to the Ethics committee and MHRA in accordance with the IRAS guidelines. Amendments and information with regards to changes in study status must be sent to R&I, (this includes changes to the local study team). Within 35 days from the receipt of a valid amendment submission, the R&I department will inform you if the amendment cannot be implemented locally. If no objections are raised NHS permission is valid and the amendment may be implemented.

When submitting documents for studies adopted into the NIHR portfolio please send the information to the Clinical Research Network: East Midlands (CRN:EM) CSP.CRNEastMidlands@NIHR.ac.uk.
When submitting documents for all other studies please use the email address rdamend@nuh.nhs.uk.

3. Ensuring all study personnel, not employed by the Nottingham University Hospitals NHS Trust hold either honorary contracts/letters of access with this Trust, before they have access to any patients or staff, their data, tissue or organs or any NUH facilities.

4. For initiating and delivering research in accordance with the Department of Health's Plan for Growth. The first patient, first visit should occur within 70 days from the receipt of a valid submission in R&I. This applies to all studies where :
 - i. The research is classed as a "clinical trial "on the IRAS filter page (first 4 categories)
5. Ensuring the research team via an identified individual, collaborates with the department of R&I and the CRN:EM in reporting recruitment data using Documas and the CRN EM Study Tracker.
6. Ensuring that for GTAC-approved studies, the NHS permission is forwarded to GTAC via the sponsor. GTAC should then issue a site authorisation letter which must be received by each site prior to recruitment commencing. A copy of this letter must be forwarded to R&I.
7. Comply with requests from NUH R&I to allow monitoring of research to comply with the Research Governance Framework and other applicable regulations.
8. Record all types of adverse events (including Suspected Unexpected Serious Adverse Drug Reaction - SUSARS) in the patient medical records and study documentation and report to the sponsor as required by the protocol.
9. Report any Serious Breach of the UK Clinical Trial regulations in connection with the trial or Serious Breach of the protocol, immediately after becoming aware of the breach to the study sponsor.
10. Reporting any changes to the study to R&I by letter or e mail. These should not be implemented until agreed with R&I.

For NUH sponsored studies only, the Chief Investigator is responsible for:

- i. All duties as detailed in the "Clinical Trial Delegation of Sponsorship responsibilities to Chief Investigator" agreement.
- ii. Contacting the sponsor for review of all amendment documentation prior to submission to the HRA and MHRA. Please note that according to HRA and MHRA regulations, all submissions of amendments need to be signed by the authorised sponsor's representative. All relevant documentation should be emailed to rdamend@nuh.nhs.uk.
- iii. Sending copies of the completed Annual Progress Reports, Development Safety Update Reports, and End of Study report required by the Ethics Committee and the MHRA (if appropriate) to the sponsor researchsponsor@nuh.nhs.uk.
- iv. Notifying NUH R&I of all SAEs by completing and sending the "Serious Adverse Event reporting form" to R&I (only via fax, e-mail or by hand), within 24hrs of becoming aware of the event. Further guidance can be found in the R&I Adverse Event SOP (SOP-RES-019).
- v. Reporting any Serious Breach of the UK Clinical Trial regulations in connection with the trial or Serious Breach of the protocol, immediately after becoming aware of the breach to NUH R&I as sponsor. Fur-

ther guidance can be found in the R&I Non Compliance and Serious Breach Reporting SOP (SOP-RES-017).

This approval letter constitutes a favourable Site Specific Assessment (SSA) for this site.

If you have any queries regarding the milestones or points detailed in this letter, please contact the Research Project Manager responsible for managing the performance of the study at NUH. This information is available on <http://nuhrise.org>.

Please note that the R&I department maintains a database containing study related information, and personal information about individual investigators e.g. name, address, contact details etc. This information will be managed according to the principles established in the Data Protection Act.

Yours sincerely,



Dr Brian Thomson / Dr Maria Koufali
Director of Research and Innovation / Deputy Director Research and Innovation

APPENDIX 3. PARTICIPANT INFORMATION SHEET AND CONSENT FORM



Knee synovial changes detected by ultrasound in the general population

Participant Information Sheet

Chief Investigator: Michael Doherty, Professor of Rheumatology

We would like to invite you to take part in our research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like further information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to determine the characteristics of certain ultrasound-detected features (the amount of fluid in the knee cavity, the thickness of the soft joint lining synovium, and the amount of blood flow in the lining) in knees of men and women of different ages from the general population of the East Midlands. To do this, an ultrasound scan and x-rays of both knees will be undertaken at a single hospital appointment in 200 volunteers from the community. These volunteers will be invited from a large community sample of people who responded to a postal questionnaire about knee health and general health. The research nurse will also ask a few simple questions about current health, smoking history and any current drug treatments, and measure blood pressure, since certain aspects of heart and cardiovascular disease may also influence the amount of pain that people experience.

An ultrasound scan is a valuable and very safe imaging method to examine knee joints for the presence of any increased joint fluid (an "effusion"), thickening of the soft joint lining (the synovium), and increased blood flow within the synovium (synovial perfusion) - all of which reflect joint inflammation. It remains unclear as to whether inflammation contributes directly to knee pain in people with knee osteoarthritis (OA), because these signs may be found not only in knees with OA but also in some people without knee pain or any x-ray changes of OA. Furthermore, although ultrasound is used widely

by doctors to improve the diagnosis of a wide range of different types of arthritis, we still do not know what is the average amount of fluid or thickness of joint lining in people from the general population, and whether this changes normally with age, differs between men and women, or differs between right and left knees. This makes it difficult to be sure as to which measures of fluid or thickening of the synovium in an individual person are truly abnormally increased above what would be expected in a normal knee of someone of the same age and gender from the same population.

We hope that the results of this study will lead to a better understanding of the variation in synovial changes in people over 40 years old which may be further used to improve the diagnosis of synovial abnormalities in people with knee pain or arthritis.

Why have I been invited?

You have already very kindly completed and returned a postal questionnaire about your general health and specifically your knee health (the Nottingham Knee Pain in the Community Study). In this you indicated that you have agreed to for us to keep your details on a database and contact you to inform you about future related research studies undertaken by the University of Nottingham. By indicating that you wished to receive more information, you did not agree to participate in this study. You should read this information sheet in detail before deciding whether you wish to take part or not. We need to recruit 200 individuals for this part of the study.

Do I have to take part?

No. You should only take part in this study if you want to. It is entirely up to you whether or not you wish to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form when you attend for the knee ultrasound scan and knee x-rays. You are free to withdraw at any time, without having to give a reason. This in no way will influence the medical care you receive from your General Practitioner (GP) or local hospital, or in any way affect your legal rights.

What will happen to me if I take part?

If you inform us that you are happy to take part in this study, you will be contacted by the research team to arrange a single appointment to attend the Nottingham City Hospital to see a research nurse. This initial appointment will take around 1.5 hours. You will be given the opportunity to ask any questions you have about the study before being asked to sign a consent form. The following assessments will then be undertaken:

- ***Ultrasound***

An ultrasound machine will be used to image both your knee joints for any underlying inflammation or swelling. This is a non-invasive procedure; it does not involve any exposure to ionizing radiation and has no detrimental side effects.

- ***X-rays of your knees***

You will also be asked to visit the X-ray Department at the Nottingham City Hospital to have x-rays of both your knees. If you have had your knees X-rayed in the past twelve months in Academic Rheumatology, as part of the Knee Pain in the Community Study or other related studies, then we will not need to repeat the x-rays again for this study (instead we will use the information obtained from your previous x-rays).

- ***Blood pressure check***

Blood pressure will be measured twice using an electronic upper arm device.

What are the possible disadvantages and risks of participating in this study?

If you are participating in this trial you will have x-rays taken of your knees. Exposure to x-rays brings a small risk of causing cancer some years in the future. In this trial you will receive more radiation exposure than for x-rays taken for standard care, but this still amounts to the equivalent of less than a day of background radiation. This means that the risk is small enough to be considered trivial.

What are the possible benefits of taking part in this study?

You will not benefit directly from participation in this study but the results from the study may allow us to better understand the normal ranges of ultrasound-detected synovial changes in people from the general population. This may subsequently lead to better assessment and possibly better management of people with painful knees.

What will happen if a problem is found during examination?

All x-ray or ultrasound findings will be explained to you at the examination. If it is felt that these findings are important for your medical care, and might be useful to share with your General Practitioner (GP), then this will be explained and discussed fully with you at the appointment. Professor Doherty will only write to your GP to inform him of the ultrasound examination and x-rays findings if you confirm that you are happy for him to do so.

Involvement of your General Practitioner/Family doctor (GP)

All the procedures outlined above are being carried out for research purposes only and your GP will not routinely be informed of your participation in the study.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your

questions. The researchers contact details are given at the end of this information sheet.

If you remain unhappy, and wish to complain formally, the Patient Advice and Liaison Service provide a confidential service and can also advise you regarding the National Health Service (NHS) complaints procedure. You can contact them by calling 0800 183 0204 (Free phone) or writing an email PALS@nuh.nhs.uk.

Will my taking part in the study be kept confidential?

If you join the study, data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

The results of the study will be published in the medical literature, but your identity will not be revealed.

We will ask for your permission to store your personal details on a secure database within Academic Rheumatology to enable us to invite you to take part in future research studies. If this happens, you will be given the opportunity to decide whether you would like to take part or not. If you state that you do not wish to be contacted regarding future studies your personal details will be destroyed when the results from the study have been analysed.

X-rays will be stored electronically on the Nottingham University Hospital system. The images would be available for review if required for clinical purposes only by other doctors and clinicians based at the Nottingham City Hospital and the Queen's Medical Centre (QMC) campus.

All research data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality and only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?

Your participation in the study is entirely voluntary and you are free to withdraw at any time, without giving reason, and without your legal rights being affected. If you withdraw then the information collected

so far cannot be erased and this information may still be used in the project analysis.

Will I be paid for participation in this study?

The study is entirely voluntary. You will receive no payment for your participation, however all your travel costs to and from the City Hospital will be reimbursed.

What will happen to the results of the research study?

We hope that the results of this study will lead to a better understanding of the normal variation in ultrasound-detected synovial changes and help guide future diagnosis of people with knee problems. Results from the study will be submitted for publication in scientific and medical journals and presented at medical scientific meetings. We will also provide you with a summary of the results if you wish.

Who is organising and funding the research?

This study is organised by members of staff in Academic Rheumatology, a department of the University of Nottingham based at the City Hospital. The study is being funded by Academic Rheumatology here at the University of Nottingham.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Nottingham-1 Research Ethics Committee.

Further information and contact details:

Study Contact: If you have any concerns or questions about any aspect of the study, you should ask to speak to Aliya Sarmanova, who will do her best to answer your questions (telephone number: 0115 82 31759, email: Aliya.Sarmanova@nottingham.ac.uk).

Chief Investigator: Professor Michael Doherty, Professor of Rheumatology, Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB, (telephone number: 0115 8231756, email: Michael.Doherty@nottingham.ac.uk).

Thank you for taking the time to read this information sheet.

CONSENT FORM

Knee synovial changes detected by ultrasound in the general population

Chief Investigator: Prof Michael Doherty

REC ref: 15/EM/0529

Name of Researcher:

Name of Participant:

ID

**Please
initial below**

1. I confirm that I have read and understand the information sheet version 2.0 dated 4th of April 2016 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.
3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.
4. I understand that participating in this study involves having an x-ray of my knees to determine the presence and severity of any osteoarthritis in the joints.
5. I understand and agree that an Ultrasound scan of both my knees will be taken to evaluate the presence of any inflammation in these joints.
6. I agree that the information gathered about me can be stored by The University of Nottingham in the Clinical Sciences Building for possible use in future studies relating to pain and/or osteoarthritis. I understand that some of these studies may be carried out by researchers other than the current team led by Professor Doherty who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in anyway. (Optional)
7. I understand that my GP will not routinely be informed of my participation in the study but agree to my GP being informed of findings which will benefit my future medical care (Optional).
8. I agree to participate in the above study.

Name of participant	Signature of participant	Date
Name of researcher	Signature of researcher	Date

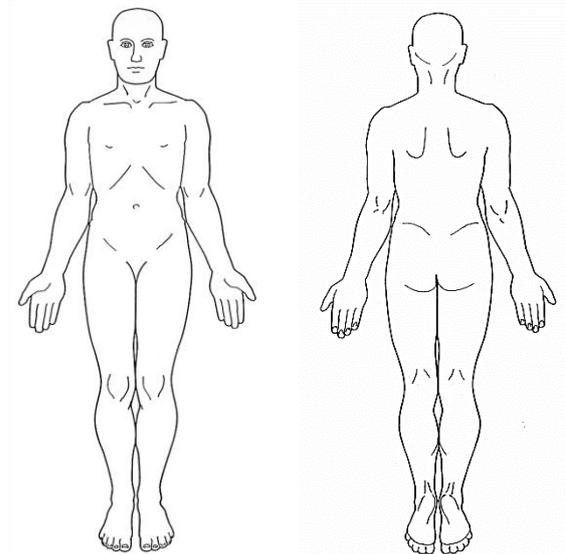
APPENDIX 4. LIST OF PRACTICES INCLUDED IN THE KPIC STUDY

1. Family Medical Centre
2. Keyworth Medical Practice
3. Rivergreen Medical Centre
4. Hucknall Road Medical Centre
5. Churchfields Medical Practice
6. Heartwood Medical Practice
7. Collingham Medical Centre
8. Church Walk Surgery
9. The Park Surgery
10. Gladstone House surgery
11. Hill View Surgery
12. Bilsthorpe Surgery

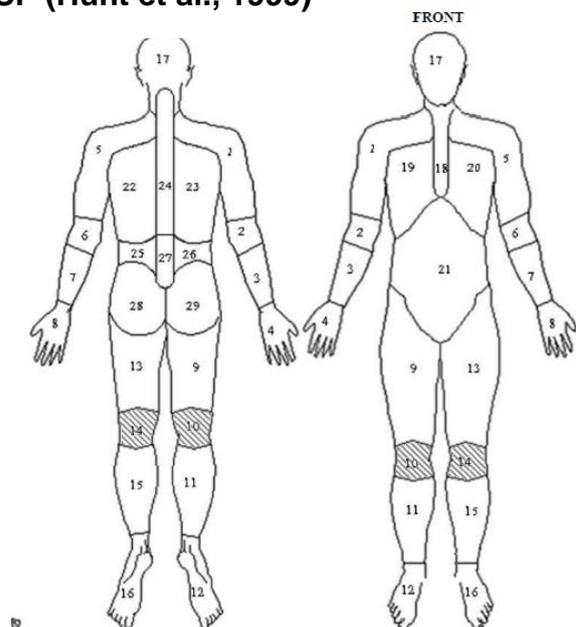
APPENDIX 5. DIAGRAMMATIC MANNEQUIN AND SCORING FOR WSP

1) Original question and mannequin in the questionnaire

This question is about **recent pain** you may have had in **any part of your body**. Please shade in the diagram below to indicate where you have suffered **any pain for most days in the previous month**. By pain we also mean aching, discomfort and/or stiffness. Please **do not include** pain due to feverish illness such as flu. If you **do not have any body pain** that has lasted one day or longer in the last 4 weeks, please tick this box and move to **SECTION 7**.



2) Coding sheet for WSP (Hunt et al., 1999)



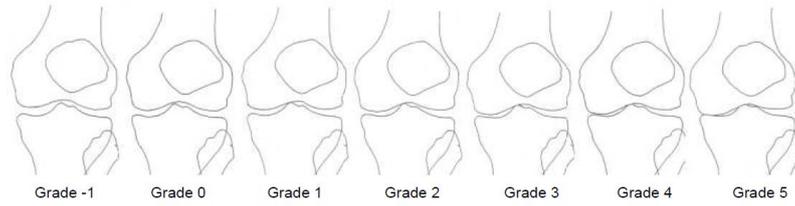
APPENDIX 6. HIGH RISK OCCUPATION CATEGORY, FILTER SEARCHES AND LINKS TO SUPPORTING LITERATURE

Agreed High Risk Category	Filter Searches	Supporting Literature
Auto-Industry/Mechanic	Car Fitter, Car Seat Assembly, Paint Sprayer/Car Repair (seat assembler, reconditioning, painting), car mechanic, car repairer, Panel beater	Coggon et al. (2000) "Occupational physical activities and osteoarthritis of the knee" \occupational activities (OA of the knee) Journal articles\Nursery profession(squatting and kneeling)\Coggon et al-2000-Arthritis & Rheumatism.pdf
Tradesmen: Construction	Brick, Build, Property, Construction, Scaffold, Damp, Ground worker, Quarry worker/operative, roof, Joiner, Carpenter, Wood, Fitter, Sign maker, Furniture design and manufacture, Upholsterer, Cabinet Maker, Shop Fitter, Window, Glazing, Glazier, Double Glazier	<p>Coggon et al. (2000) "Occupational physical activities and osteoarthritis of the knee" \occupational activities (OA of the knee) Journal articles\Nursery profession(squatting and kneeling)\Coggon et al-2000-Arthritis & Rheumatism.pdf</p> <p>Susan Andersen et al. (2012) "Cumulative years in occupation and the risk of hip or knee osteoarthritis in men and women: a register-based follow-up study" \occupational activities (OA of the knee) Journal articles\Susan Andersen et al. -Cumulative years in occupation HCA's.pdf</p> <p>Department of Social Security (1995) "Disorders of the Knee" Report \occupational activities (OA of the knee) Journal articles\Disorders of the knee - Department of social security.pdf</p>
Tradesmen: Other	Electric, Jointer Electrical, Lineman, Panel wirer/wireman, Carpet, Floor, Slab, Paint, Plaster, Cabinet Sprayer, Plumber, Pipe Fitter	<p>Coggon et al. (2000) "Occupational physical activities and osteoarthritis of the knee" \occupational activities (OA of the knee) Journal articles\Nursery profession(squatting and kneeling)\Coggon et al-2000-Arthritis & Rheumatism.pdf</p> <p>Susan Andersen et al. (2012) "Cumulative years in occupation and the risk of hip or knee osteoarthritis in men and women: a register-based follow-up study" \occupational activities (OA of the knee) Journal articles\Susan Andersen et al. -Cumulative years in occupation HCA's.pdf</p> <p>Department of Social Security (1995) "Disorders of the Knee" Report \occupational activities (OA of the knee) Journal articles\Disorders of the knee - Department of social security.pdf</p>
Emergency Services	Police, Firefighter, Army, Soldier, National Service, RAF, Marines, Navy, Naval, Paratrooper, Royal (air force etc.), Ambulance, Paramedic, Military, WRNS (Women's Royal Navy Service)	
Factory/Warehouse Worker	Factory, Workshop, Worker, Assembly, Production, Warehouse, Picker, Packer	Palmer K, 2012 Occupations activities and osteoarthritis of the knee Br Med Bull. 2012 Jun; 102: 147-170. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428837/
Land management/ Cultivation	Agriculture, Agricultural, Farm, Farmer, "Picker (fruits)", Herdsman, Dairy man, Gardener, Green, Landscape, Lawn, Horticulture, Groundsman, Greenkeeper, Horticulturalist, Timber yard worker, forest worker, forester, forestry	<p>Coggon et al. (2000) "Occupational physical activities and osteoarthritis of the knee" \occupational activities (OA of the knee) Journal articles\Nursery profession(squatting and kneeling)\Coggon et al-2000-Arthritis & Rheumatism.pdf</p> <p>Susan Andersen et al. (2012) "Cumulative years in occupation and the risk of hip or knee osteoarthritis in men and women: a register-based follow-up study" \occupational activities (OA of the knee) Journal articles\Susan Andersen et al. -Cumulative years in occupation HCA's.pdf</p>

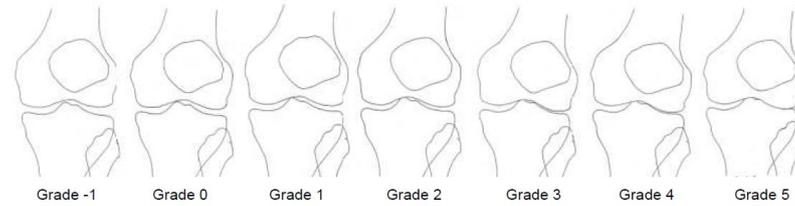
Manual Workers Engineering	Engineer, Millwright, Lagger (Insulators)/ Lagging	Department of Social Security (1995) "Disorders of the Knee" Report. \occupational activities (OA of the knee) Journal articles\Disorders of the knee - Department of social security.pdf
Health Services	Nurse, Nursing, carer, care worker, care assistant, support worker, Home help, RGN (registered general nurse), RNMH (registered nurse mental health), Ward Orderly, SRN (State Registered Nurse), RMN (Registered Mental Nurse), RNLD	DeputySynthes Information sheet (2015) "Hardest working knees: Occupational activities that can cause or aggravate knee osteoarthritis". \occupational activities (OA of the knee) Journal articles\Hardest working knees Information sheet.pdf Susan Andersen et al. (2012) "Cumulative years in occupation and the risk of hip or knee osteoarthritis in men and women: a register-based follow-up study". \occupational activities (OA of the knee) Journal articles\Susan Andersen et al. -Cumulative years in occupation HCA's.pdf
Coal Miner	Coal, Mine, Colliery, Down pit, Mining, Collier	Department of Social Security (1995) "Disorders of the Knee" Report. \occupational activities (OA of the knee) Journal articles\Disorders of the knee - Department of social security.pdf
Metal Worker	Steel, Weld, Metal , Blacksmith, Foundry, Moulder, Plater, Fabricator	Coggon et al. (2000) "Occupational physical activities and osteoarthritis of the knee". \occupational activities (OA of the knee) Journal articles\Nursery profession(squatting and kneeling)\Coggon et al-2000-Arthritis & Rheumatism.pdf
PCM (Porters, Cleaners, Maintenance)	Porter, Clean Window, Cleaner, Valet, Wash (Car), Janitor, Domestic Assistant, Chambermaid, Hospital domestic, domestic, caretaker, building maintenance, maintenance, handyman, building assistant	Coggon et al. (2000) "Occupational physical activities and osteoarthritis of the knee". \occupational activities (OA of the knee) Journal articles\Nursery profession(squatting and kneeling)\Coggon et al-2000-Arthritis & Rheumatism.pdf Department of Social Security (1995) "Disorders of the Knee" Report. \occupational activities (OA of the knee) Journal articles\Disorders of the knee - Department of social security.pdf
PE Teacher	PE, Physical	Department of Social Security (1995) "Disorders of the Knee" Report. \occupational activities (OA of the knee) Journal articles\Disorders of the knee - Department of social security.pdf
Postman	Post, mail	Agreed in Consensus Meeting due to prolonged walking, bending and lifting.
Labourer	Labourer, Pipe yard Worker, Concrete, Installer, Mason, Fibre glass, Asphalt(er), Digging trenches, Fencer, Manual	Lindberg H, Montgomery F, (1987) Heavy Labour and the occurrence of gonarthrosis, Clin Orthop 214:235 - 236 in Palmer K, 2012 Occupations activities and osteoarthritis of the knee Br Med Bull. 2012 Jun; 102: 147-170. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428837/
Road Worker	Roadworks, Road, Highway, Platelayer, Tarmac layer, Tarmac	Jarvholm B 2007 in Palmer K, 2012 Occupations activities and osteoarthritis of the knee Br Med Bull. 2012 Jun; 102: 147-170. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3428837/
Shipyard Worker	Shipwright	Coggon et al. 2000 "Occupational physical activities and osteoarthritis of the knee". \occupational activities (OA of the knee) Journal articles\Nursery profession(squatting and kneeling)\Coggon et al-2000-Arthritis & Rheumatism.pdf Department of Social Security (1995) "Disorders of the Knee" Report. \occupational activities (OA of the knee) Journal articles\Disorders of the knee - Department of social security.pdf
Sports-Other	Any , Climbing instructor, Parachute instructor	

APPENDIX 7. JOINT SPACE NARROWING AND OSTEOPHYTES SCORING EXAMPLES ACCORDING TO THE NOTTINGHAM LOGICALLY DERIVED ORDINAL LINE DIAGRAM ATLAS (NAGAOSA ET AL., 2000, WILKINSON ET AL., 2005)

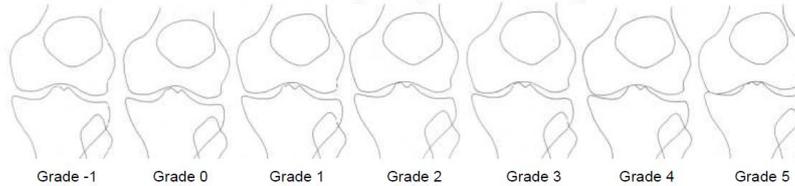
Medial tibio-femoral joint space narrowing for women



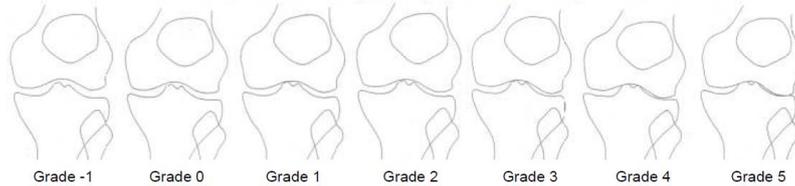
Lateral tibio-femoral joint space narrowing for women



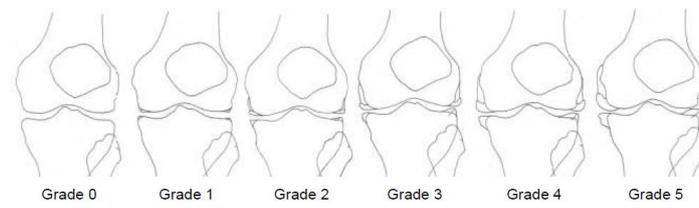
Medial tibio-femoral joint space narrowing for men



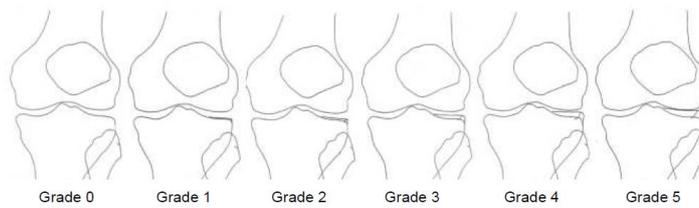
Lateral tibio-femoral joint space narrowing for men



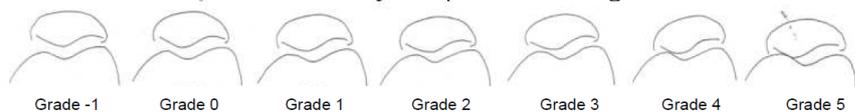
Osteophytes in all tibio-femoral sites



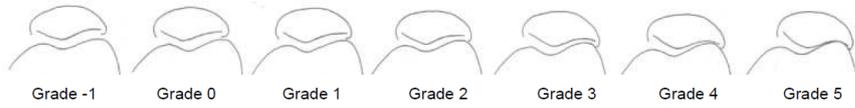
Lateral tibial osteophytes (optional shape)



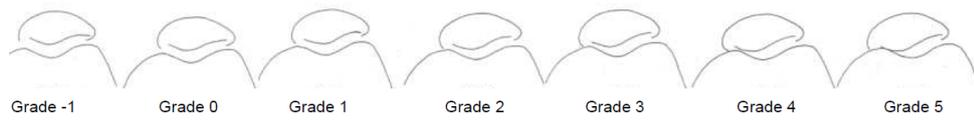
Medial patella-femoral joint space narrowing for women



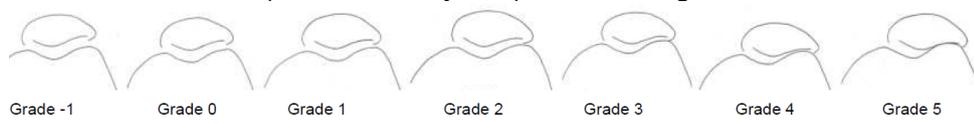
Lateral patella-femoral joint space narrowing for women



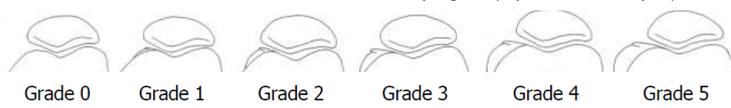
Medial patella-femoral joint space narrowing for men



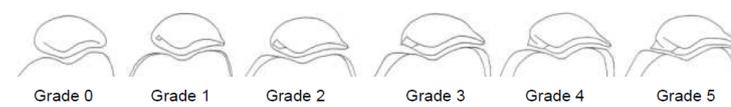
Lateral patella-femoral joint space narrowing for men



Medial femoral trochlear osteophyte (optional shape)



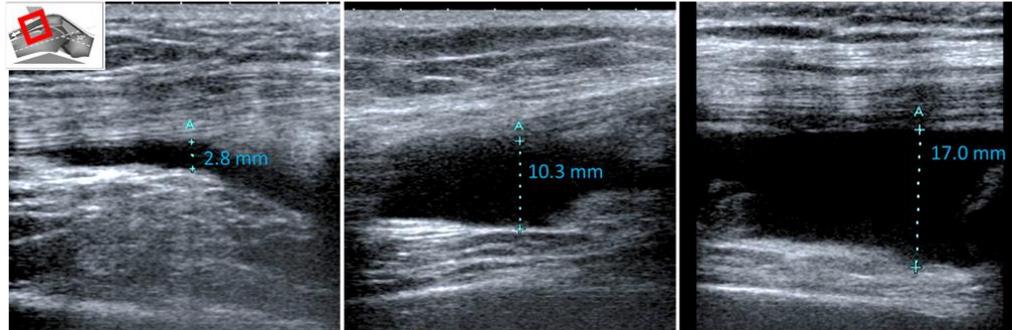
Osteophytes in all patello-femoral sites



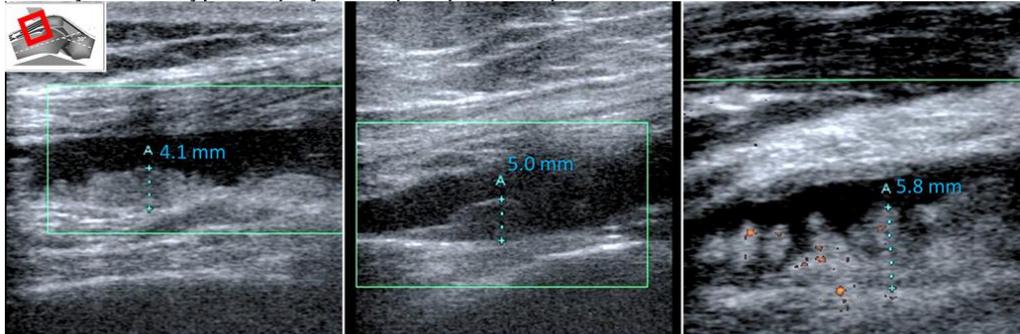
Note: For convenience, the atlas illustrations are reproduced in reduced size. The scoring of radiographs was based on the atlas in the correct size (printed version available at Academic Rheumatology Department)

APPENDIX 8. GREY-SCALE US IMAGES OF EFFUSION AND SYNOVIAL HYPERTROPHY IN THE SUPRA-PATELLAR POUCH, AND POWER DOPPLER SIGNAL IN THE LATERAL TIBIO-FEMORAL SPACE OF THE KNEE (ADDITIONAL EXAMPLES)

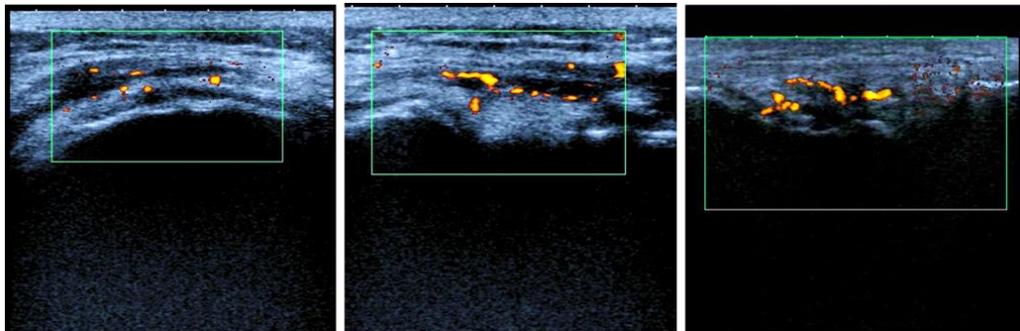
A. Effusion in supra-patellar pouch



B. Synovial hypertrophy in supra-patellar pouch



C. Power Doppler signal in the medial tibio-femoral space



APPENDIX 9. SUMMARY ON PREVALENCE OF EFFUSION, SYNOVIAL HYPERTROPHY AND DOPPLER SIGNAL IN PEOPLE WITH KNEE PAIN AND OSTEOARTHRITIS AND ITS ASSOCIATION WITH PAIN

Author, year	Source of population	Group characteristics	N	Mean age (SD/ range)	Women, %	K&L≥2, %	Mean pain score (SD)	Knee effusion		Synovial hypertrophy			Doppler Signal, %	
								Threshold in mm	Prevalence, %	Depth in mm, mean (SD)	Threshold in mm	Prevalence, %		Depth in mm, mean (SD)
Cross-sectional studies														
<i>Knee pain</i>														
Kumm, 2009	community	duration ≥3 month	106	49 (36-58)	68.87	12.26		4	25.47		4	31.13		5.66
Picerno, 2013	hospital	>18 years old	399	56.2 (16.3)	74.94			2	62.91					
Arthul, 2014	hospital		276					+/-*	7.97					
<i>Symptomatic OA</i>														
Bevers, 2014	hospital		180	57 (9.2)	66.67	60	61 (17)	+/-*	10.91		2	20.56		
Chan, 2014	community	>40 years old	193	59 (13.9)	74.09	61.14	56 (25)	4	32.2	6.73 (4.3)	4	37.82	4.36 (2.2)	
D'Agostino, 2005	hospital	>18 years old, duration >6 month, K&L 1-4, pain last 48 hours ≥30 mm	600	66.7 (9.8)	72.5		63 (18.5)	4	43.5	4.0 (4.6)	4	16.67	2.1 (2.5)	
Ulasli, 2014	hospital	>30 years old	86	56.2 (10.2)	80.23		65.2 (11.7)	4	73.84	4.38**				
Mendieta 2006	hospital	pain≥30 mm	81	66.75 (8.67)	96.3	93.83		2	79.01					
Malas, 2014	not declared		61	58.88 (7.2)	83.61	-		+/-*	29.51					
Iagnocco, 2014	hospital	duration>6 month, pain ≥20 mm	82	63.2 (8.1)	64.63	-	48.4 (19.9)	+/-*	42.68		+/-*	21.95	-	2.44
<i>Radiographic OA</i>														
Mendieta 2006	hospital		20	62.1 (9)	70	65		2	35					

Author, year	Source of population	Group characteristics	N	Mean age (SD/range)	Women, %	K&L≥2, %	Mean pain score (SD)	Knee effusion		Synovial hypertrophy			Doppler Signal, %	
								Threshold in mm	Prevalence, %	Depth in mm, mean (SD)	Threshold in mm	Prevalence, %		Depth in mm, mean (SD)
Case-control studies														
<i>Knee pain</i>														
Blankstein, 2006	not declared		110	51 (35-68)	-	-		+/-*	10.91		+/-*	6.36		
Hall 2014	community		59	63.8 (8.8)	55.93	-	48.9 (22)	4	32.2	3.4 (3.2)	4	11.86	1.0 (1.9)	3.39
<i>Symptomatic OA</i>														
Hall, 2014	community	K&L≥2, pain≥30mm	62	73.9 (7.8)	67.74	100	48.2 (24.6)	4	91.94	8.1 (4.0)	4	82.26	6.7 (3.3)	16.13
Naredo, 2005	hospital		50	64.3 (7.9)	88	-		4	42	-				
Zivanovic, 2009	military academy	duration>6 month	88	69.97 (9.37)	77.27	-		4	75	11.38 (4.44)	4	67.05	6.09 (2.8)	
Wu, 2012	hospital	equal K&L in both knees, pain ≥40 mm	56	62.9 (8.2)	75	98.21		4	27.68	-	4	83.93	-	
Tarhan, 2003	not declared	>45 years old, pain within 4 weeks	58	57.4 (8.5)	82.76	-	58.9 (20.2)	2	67.24	-	2	32.76	-	
Chatzopoloulos, 2008	hospital	consulted for radiation synovectomy	196	69 (49-87)	74.49	-		2	84.69	-				
Jung, 2006	hospital		51	62	96.08	-	50	2	49.02	-				
Song, 2009	hospital	K&L≥2, duration>6 month, pain ≥40mm	41	65 (6.7)	63.41	100	68.3 (19.6)	2	78.05	6.1 (2.8)	4	17.07	1.9 (1.9)	58.54
Svetlova, 2010	hospital	duration 2-36 month, K&L 0-2	308	46.2 (11.5)	78.25	30.52	60.13 (15.62)	+/-*	29.55					

Author, year	Source of population	Group characteristics	N	Mean age (SD/range)	Women, %	K&L≥2, %	Mean pain score (SD)	Knee effusion		Synovial hypertrophy			Doppler Signal, %	
								Threshold in mm	Prevalence, %	Depth in mm, mean (SD)	Threshold in mm	Prevalence, %		Depth in mm, mean (SD)
Kristoffersen, 2006	community	>50 years old, pain ≥40 mm, osteophytes on x-ray	71	68 (35-88)	76.06	-		+/-*	85.92	-	+/-*	100		73.24
Tchetina, 2013	hospital	postmenopausal women, K&L≥2, pain ≥40 mm	47		100	100	(40-70)				4	48.94		
Beitinger, 2013	hospital	scheduled for TKR	72	68	-									95.83
Walther, 2001	hospital	scheduled for TKR	13	72.1	61.54									69.23
Radiographic OA														
Hall, 2014	community		32	73.1 (7.9)	59.38	100	7.2 (14.4)	4	81.25	6 (2.8)	4	40.63	3.9 (3.9)	6.25
General/normal population														
Abraham, 2014	community	population-based (the Newcastle thousand families birth cohort)	311	63 (61-63)	55.31			4	24					
D'Agostino, 2015	community	population-based (the Bruneck cohort)	488	72.57 (8.53)	53.48			+/-***	60.4		+/-***	66.59		24.83
Martino, 1992	not declared	healthy volunteers	50	37 (14-58)	34					2.6 (1-4 mm) (effusion plus thickening)				

Author, year	Source of population	Group characteristics	N	Mean age (SD/ range)	Women, %	K&L≥2, %	Mean pain score (SD)	Knee effusion		Synovial hypertrophy			Doppler Signal, %	
								Threshold in mm	Prevalence, %	Depth in mm, mean (SD)	Threshold in mm	Prevalence, %		Depth in mm, mean (SD)
Mielke, 1990	not declared	healthy volunteers	56	(21-75)						2.0 (0.4)			1.7 (0.3)	
Schmidt, 2004	not declared	white volunteers	102	38.4 (20-60)	52.94					2.4 (1.25)			2.4 (1.2)	
Control groups														
Hall, 2014	community	people recruited from community-based studies (No pain, no X-ray changes)	90	71 (7.9)	70	0	6.6 (11.0)	4	28.88	2.6 (2.7)	4	7.78	0.7 (1.5)	2.22
Naredo, 2005	hospital	Healthy without knee pain (X-ray assessment was not reported)	10	68 (9.4)	80			4	0	2.3 (0.7)				
Tarhan, 2003	not declared	Healthy without knee pain (X-ray assessment was not reported)	16	59.1 (9.8)	75			2	16.13		2	0		
Beitinger, 2013	hospital	healthy volunteers (age, sex- adjusted)	52					+/-***	5.77		+/-***	3.85		

Note: * - reported prevalence as absent or present; ** - SD was not provided; *** - reported prevalence as absent or present.

DS – Doppler signal; K&L - Kellgren and Lawrence; SD- standard deviation.

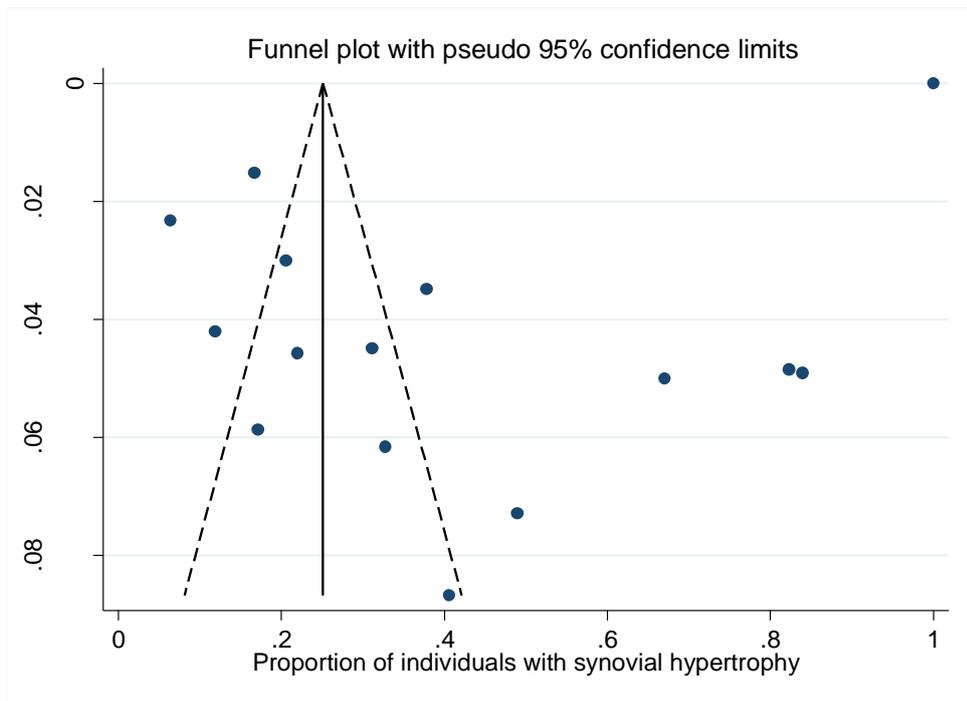
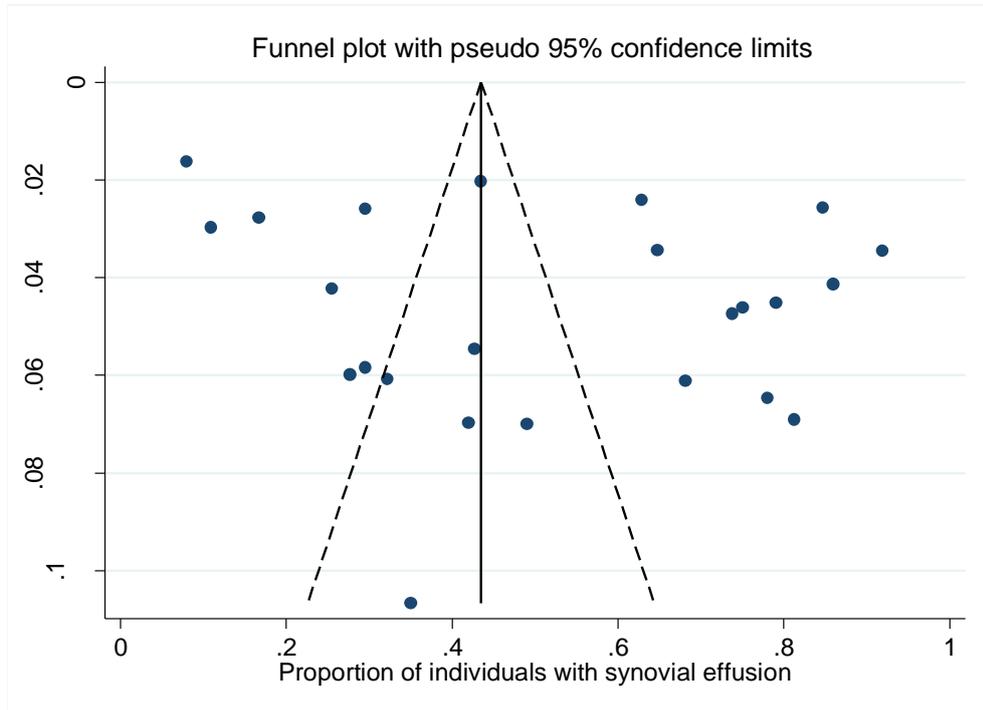
APPENDIX 10. SUMMARY OF STUDIES INCLUDING STUDY DESIGN AND SCORING SYSTEM FOR ULTRASOUND-DETECTED PATHOLOGY

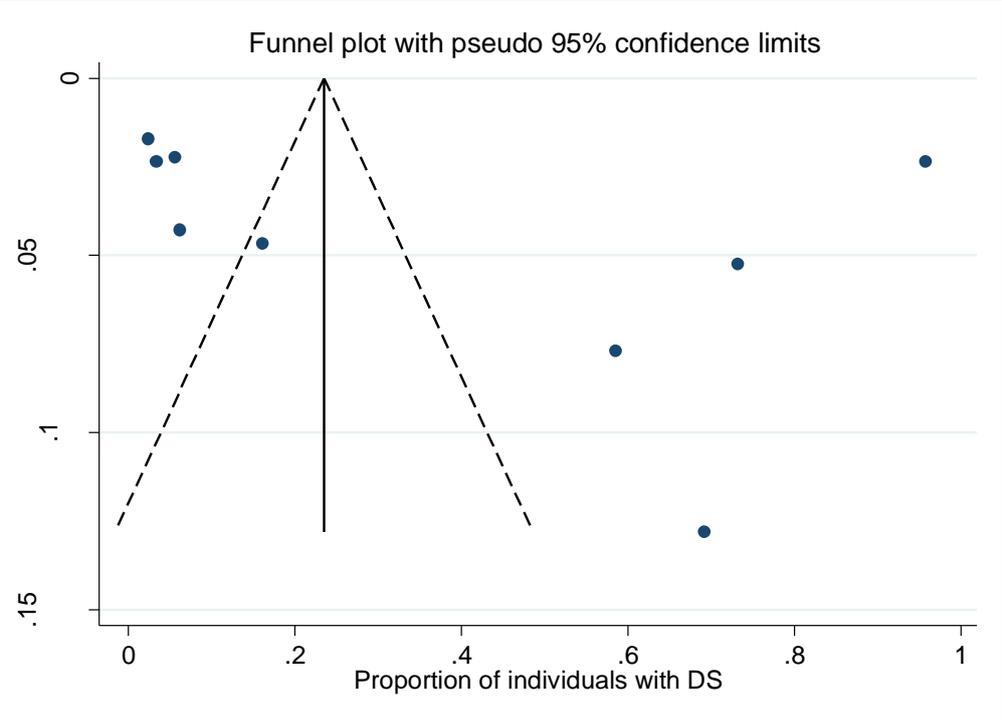
Author, year	Study design	Scoring system			US assessment characteristics	
		Effusion	Synovial hypertrophy	Doppler signal	Suprapatellar area	Knee position
Beitinger, 2013	Case-control	-	-	Colour Doppler (summative score 0-12 from supra-, infra-patellar, medial and lateral scan (grades 0-3 for each))	-	-
Bevers, 2014	Cross-sectional	≥4mm	≥2mm	-	Midline	Neutral
Chan, 2014	Cross-sectional	≥4mm	≥4mm	-	-	-
Chatzopoloulos, 2008	Case-control	≥2mm (absent <2mm, small 2-5 mm, large >5mm)	-	-	-	30-40° of flexion
D'Agostino, 2005	Cross-sectional	≥4mm	≥4mm	-	Midline	45° of flexion
Hall, 2014	Case-control	≥4mm	≥4mm	Power Doppler (grades 0-3: normal/absent, mild, moderate, marked/severe)	Multi-planar	30° of flexion
Jung, 2006	Case-control	≥2mm	-	-	-	Neutral
Kumm, 2009	Cross-sectional	≥4mm	≥4mm	Doppler (presence/absence)	-	-
Mendieta 2006	Cross-sectional	≥2mm	-	-	Midline	30° of flexion
Naredo, 2005	Case-control	≥4mm	-	-	-	30° of flexion
Picerno, 2013	Cross-sectional	≥2mm	-	-	Multi-planar	Neutral
Song, 2009	Case-control	≥2mm (grades 0-3: normal (< 5 mm), slight (5-7 mm), moderate (8-10 mm), strong (≥11 mm))	≥4mm (grades 0-3: normal (0mm), slight (>0 to <4 mm), moderate (4-7 mm), strong (≥8 mm))	Power Doppler (grades 0-3: normal/absent, mild, moderate, marked/severe)	Multi-planar	Less than 90° of flexion

Author, year	Study design	Scoring system			US assessment characteristics	
		Effusion	Synovial hypertrophy	Doppler signal	Suprapatellar area	Knee position
Tarhan, 2003	Case-control	≥2mm (grades 0-3: absent (<2 mm), mild (2-4 mm), medium (5-10 mm), severe (>10 mm))	≥2mm (grades 0-3: absent (<2 mm), mild (2-5 mm), medium (6-8 mm), severe (>8 mm))	-	Multi-planar	Neutral
Tchetina, 2013	Case-control		≥4mm	-	-	-
Ulasli, 2014	Cross-sectional	≥4mm (grades 0-3: grade 0 (< 4 mm), grade 1 (4-8 mm), grade 2 (8-10 mm), grade 3 (≥11 mm))	-	-	Multi-planar	30° of flexion
Walther, 2001	Case-control	-	-	Power Doppler (grades 0-3: normal/absent, mild, moderate, marked/severe)	Multi-planar	-
Wu, 2012	Case-control	≥4mm (grades 0-3: grade 0 (< 4 mm), grade 1 (4-8 mm), grade 2 (8-10 mm), grade 3 (≥11 mm))	≥4mm (grades 0-3: grade 0 (< 4 mm), grade 1 (4-8 mm), grade 2 (8-10 mm), grade 3 (≥11 mm))	-	Multi-planar	-
Zivanovic, 2009	Case-control	≥4mm	≥4mm		-	-
Kristoffersen, 2006	Case-control	Absent/present	Absent/present	Colour Doppler (absent/present)	Multi-planar	-
Arthul, 2014	Cross-sectional	Absent/present	-	-	-	-
Blankstein, 2006	Case-control	Absent/present	Absent/present		Multi-planar	-
Iagnocco, 2014	Cross-sectional	Absent/present (grades 0-3: normal, mild, moderate, marked/severe)	Absent/present (grades 0-3: normal, mild, moderate, marked/severe)	Power Doppler (grades 0-3: normal/absent, mild, moderate, marked/severe)	-	-
Malas, 2014	Cross-sectional	Absent/present	-	-	-	-

Author, year	Study design	Scoring system			US assessment characteristics	
		Effusion	Synovial hypertrophy	Doppler signal	Suprapatellar area	Knee position
Svetlova, 2010	Case-control	Absent/present (grades 0-3: absent (0 mm), mild (≤ 3 mm), medium (4-6 mm), severe (> 6 mm))	-	-	Multi-planar	-
Abraham, 2014	Cross-sectional	≥ 4 mm	-	-	Multi-planar	30° of flexion
D'Agostino, 2015	Cross-sectional	Absent/present (grades 0-3)	Absent/present (grades 0-3)	Absent/present (grades 0-3)	Multi-planar	Different degrees of flexion
Martino, 1992	Cross-sectional	-	-	-	-	Neutral
Mielke, 1990	Case-control	-	-	-	-	-
Schmidt, 2004	Cross-sectional	-	-	-	-	-

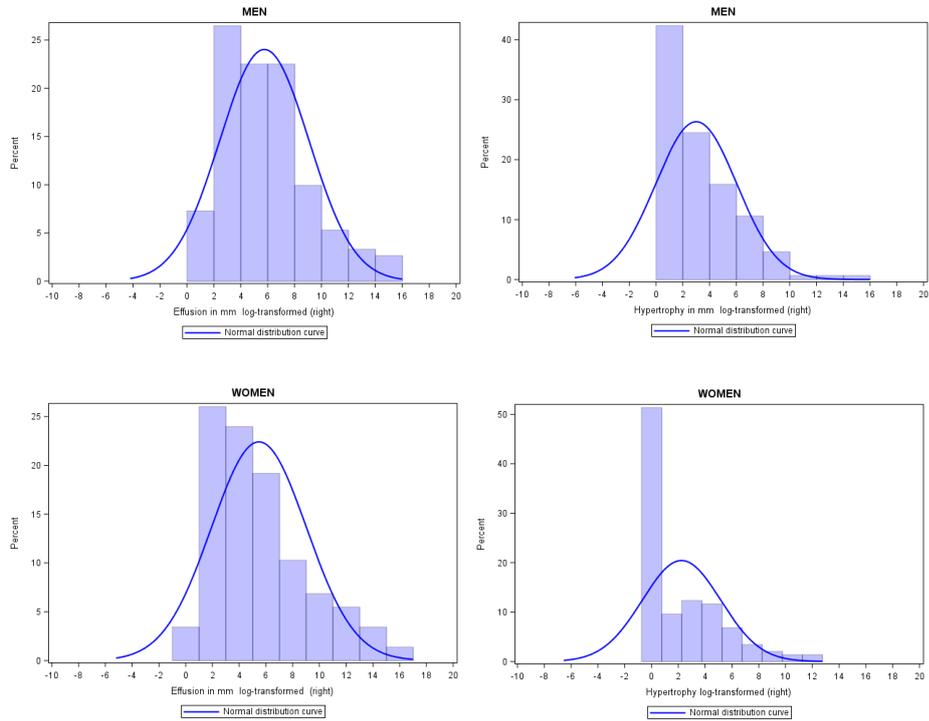
APPENDIX 11. FUNNEL PLOTS



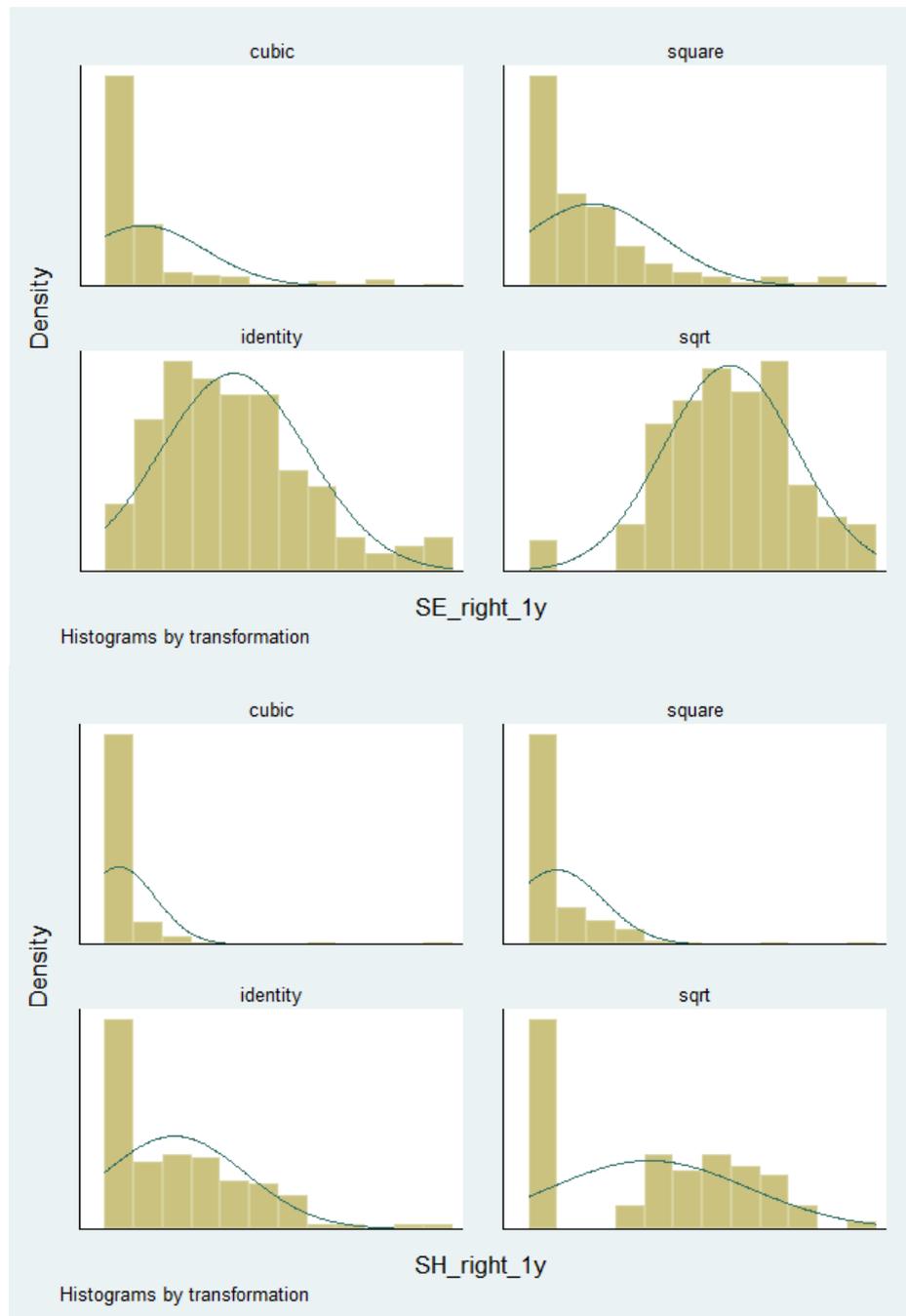


APPENDIX 12. TRANSFORMATION ATTEMPTS

1. Log-transformation



2. Other transformations



APPENDIX 13. ULTRASOUND SYNOVIAL FEATURES AND RADIOGRAPHIC OSTEOARTHRITIS AND ASSOCIATIONS WITH KNEE PAIN

	No Knee Pain	Early Knee Pain	Established Knee Pain
Effusion			
		1.78 (1.01; 3.15)	1.87 (0.91; 3.86)
$\geq 4\text{mm}$ aOR (95%CI) ¹	1	1.90 (1.07; 3.39)	1.92 (0.92; 4.00)
$\geq 4\text{mm}$ aOR (95%CI) ²	1	1.80 (1.01; 3.22)	1.77 (0.84; 3.73)
Synovial hypertrophy			
		3.17 (1.17; 8.53)	4.97 (1.66; 14.86)
$\geq 4\text{mm}$ aOR (95%CI) ¹	1	3.18 (1.18; 8.57)	5.07 (1.70; 15.12)
$\geq 4\text{mm}$ aOR (95%CI) ²	1	2.80 (1.03; 7.61)	4.28 (1.42; 12.90)
ROA			
Crude OR (95%CI)		4.43 (1.96; 9.98)	11.02 (4.65; 26.10)
aOR (95%CI) ³		4.37 (1.89; 10.13)	11.82 (4.71; 29.66)
aOR (95%CI) ⁴		2.84 (1.19; 6.80)	5.77 (2.20; 15.18)
aOR (95%CI) ⁵		2.81 (1.17; 6.75)	6.15 (2.30; 16.43)
aOR (95%CI) ⁶		2.83 (1.18; 6.83)	6.11 (2.27; 16.45)

Note: 1 - odds ratios adjusted for age, gender, BMI, quadriceps strength and radiographic OA scores.
 2 - odds ratios adjusted for age, gender, BMI, quadriceps strength, radiographic OA scores and analgesic use.
 3 - odds ratios adjusted for age, gender and BMI.
 4 - odds ratios adjusted for age, gender, BMI and synovial hypertrophy.
 5 - odds ratios adjusted for age, gender, BMI, synovial hypertrophy and quadriceps strength.
 6 - odds ratios adjusted for age, gender, BMI, synovial hypertrophy, quadriceps strength and analgesic use.

APPENDIX 14. THE PRESENCE OF COMORBIDITY

	Total	No KP	Knee pain	P-value
N	736	207	529	
Conditions				
<i>High cholesterol, n (%)</i>	201 (27.31)	49 (23.67)	152 (28.73)	0.1658
<i>Heart attack /angina, n (%)</i>	46 (6.25)	9 (4.35)	37 (6.99)	0.1823
<i>Hypertension, n (%)</i>	204 (27.72)	45 (21.74)	159 (30.06)	0.0234
<i>Diabetes, n (%)</i>	67 (9.10)	12 (5.80)	55 (10.40)	0.0511
<i>Underactive/overactive thyroid, thyroiditis, n (%)</i>	36 (4.89)	9 (4.35)	27 (5.10)	0.6689
<i>Stroke, n (%)</i>	19 (2.58)	7 (3.38)	12 (2.27)	0.3919
<i>Multiple sclerosis, n (%)</i>	0	0	0	
<i>Irritable bowel syndrome, n (%)</i>	89 (12.09)	16 (7.73)	73 (13.80)	0.0232
<i>Fibromyalgia, n (%)</i>	10 (1.36)	1 (0.48)	9 (1.70)	0.1993
<i>Chronic fatigue syndrome, n (%)</i>	4 (0.54)	1 (0.48)	3 (0.57)	0.8891
<i>Chronic obstructive pulmonary disease (COPD), n (%)</i>	5 (0.68)	0	5 (0.95)	0.1605
<i>Asthma, n (%)</i>	33 (4.48)	8 (3.86)	25 (4.73)	0.6117
<i>Idiopathic pulmonary fibrosis, n (%)</i>	1 (0.14)	1 (0.48)	0	0.1097
<i>Liver cirrhosis, n (%)</i>	1 (0.14)	0	1 (0.19)	0.5313
<i>Hepatitis, n (%)</i>	0	0	0	
<i>Non-alcogolic fatty liver disease, n (%)</i>	0	0	0	
<i>Rheumatoid arthritis, n (%)</i>	6 (0.82)	1 (0.48)	5 (0.95)	0.5308
<i>Ankylosing spondylitis, n (%)</i>	3 (0.41)	0	3 (0.57)	0.2776
<i>Lupus, n (%)</i>	1 (0.14)	0	1 (0.19)	0.5313
<i>Psoriatic arthritis, n (%)</i>	2 (0.27)	0	2 (0.38)	0.3757
Systems affected				
<i>Cardiovascular disease, n (%)</i>	307 (41.71)	76 (36.71)	231 (43.67)	0.0855
<i>Endocrine disease, n (%)</i>	99 (13.45)	21 (10.14)	78 (14.74)	0.1001
<i>Non-restorative pain disorders, n (%)</i>	97 (13.18)	17 (8.21)	80 (15.12)	0.0127
<i>Lung disease, n (%)</i>	38 (5.16)	9 (4.35)	29 (5.48)	0.5318
<i>Liver disease, n (%)</i>	1 (0.14)	0	1 (0.19)	0.5313
<i>Chronic kidney disease/failure (CKD), n (%)</i>	1 (0.14)	0	1 (0.19)	0.5313
<i>Central nervous system disorders, n (%)</i>	19 (2.58)	7 (3.38)	12 (2.27)	0.3919
<i>Gout, n (%)</i>	11 (1.49)	4 (1.93)	7 (1.32)	0.5403
<i>Chronic rheumatic conditions, n (%)</i>	12 (1.63)	1 (0.48)	11 (2.08)	0.1242

APPENDIX 15. CHARACTERISTICS OF THE STUDY SUBGROUPS

	Controls (KP- ROA ¹ - WSP ² -)	Subgroup 1 (KP+ ROA+ WSP+)	Subgroup 2 (KP+ ROA+ WSP-)	Subgroup 3 (KP+ ROA- WSP+)	Subgroup 4 (KP+ ROA- WSP-)
N	160	58	116	108	236
Age (years), mean (SD)	64.10 (10.04)	63.53 (8.83)	66.66 (9.18)	58.54 (9.72)	60.65 (9.72)
Women, n (%)	83 (51.88)	38 (65.52)	66 (56.90)	71 (65.74)	124 (52.54)
BMI (kg/m²), mean (SD)	25.63 (3.97)	31.59 (6.56)	29.70 (6.08)	29.82 (6.41)	27.79 (4.80)
Current knee pain³, n (%)		49 (84.48)	90 (77.59)	81 (75.00)	159 (67.37)
Current knee pain severity (NRS 0-10), mean (SD)		6.48 (2.39)	4.98 (2.90)	5.38 (2.81)	4.01 (2.89)
Use of analgesics					
<i>Prescribed NSAIDs, n (%)</i>	2 (1.25)	5 (8.62)	13 (11.21)	14 (12.96)	8 (3.39)
<i>Over-the-counter NSAIDs, n (%)</i>	15 (9.38)	27 (46.55)	30 (25.86)	37 (34.26)	47 (19.92)
<i>Opioids, n (%)</i>	2 (1.25)	19 (32.76)	15 (12.93)	23 (21.30)	17 (7.20)

Note: SD – standard deviation; CI – confidence interval; NSAIDs - non-steroidal anti-inflammatory drugs; NRS – numerical rating scale 0-10; BMI - body mass index.

¹ Widespread pain defined as concurrent pain experienced within the past 4 weeks axially, above and below the waist, and on both sides of the body (ACR criteria) self-reported using a diagrammatic manikin.

² Radiographic osteoarthritis defined as definite JSN (grade 2) plus definite osteophyte (grade 2) in any compartment (tibiofemoral or patellofemoral).

³ Knee pain on most days of the past month.